

RIJKSUNIVERSITEIT GRONINGEN

**CATALYSIS OF DIELS-ALDER
REACTIONS IN WATER**

Proefschrift

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It is water that, in taking different forms,
constitutes the earth, atmosphere, sky, mountain,
gods and men, beasts and birds, grass and trees,
animals down to worms, flies and ants.
All these are different forms of water.
Meditate on water !

Thales of Miletus (6th century BC)

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Introduction

This chapter introduces the experimental work described in the following chapters. Some mechanistic aspects of the Diels-Alder reaction and Lewis-acid catalysis thereof are discussed. This chapter presents a critical survey of the literature on solvent effects on Diels-Alder reactions, with particular emphasis on the intriguing properties of water in connection with their effect on rate and selectivity. Similarly, the effects of water on Lewis acid - Lewis base interactions are discussed. Finally the aims of this thesis are outlined.

1.1 Introduction

Organic chemistry has had a profound influence on the way the human society has developed. Organic reactions have been carried out by our ancestors in the preparation of food, drink, dyes and potions millennia before such preparation was recognised as a field in science. During the last two centuries the discipline has seen a tremendous growth. In our everyday life we encounter many different products that are offsprings of the incessant efforts of researchers in organic chemistry, ranging from soaps to fuels, from paints to medicines. The benefits of these compounds are obvious. However, their preparation inevitably brings with it a burden to our environment and in the end to ourselves and our children. The most effective solution to this pollution problem is a reduction of their production. As long as this is not realised, it is of utmost importance to reduce the environmental impact of our activities.

A very significant source of pollution is formed by the organic solvents, which are used in much larger quantities than the solutes they carry and have a tendency to escape into the environment through evaporation and leakage. Halogenated solvents are particularly notorious with respect to their toxic character and poor biodegradability. A lot of research is currently devoted to the development of solvent-free systems or replacement of the solvent by a less environmentally hazardous one. Water is ideally suited for this purpose owing to its non-toxic character. Its enormous abundance on this planet makes water a readily accessible alternative. There are also advantages from an economic point of view¹.

Unfortunately, from a chemical point of view, not all transformations are feasible in an aqueous solvent system. Many reagents decompose when brought into contact with water and many others are almost insoluble in this solvent. Moreover, water interacts strongly with many chemicals, thereby literally shielding them from the action of other chemicals with which they are to react. Not surprisingly, water has not been a very popular solvent among organic chemists in the past.

Fortunately, there are also a substantial number of chemical transformations that are not only compatible with an aqueous medium, but actually strongly benefit from the unique characteristics of

water. The use of an aqueous solvent can induce an increase in rate or selectivity. An aqueous solvent also permits use of a simplified reaction or work-up procedure. The increased focus on water in synthetic organic chemistry during the past few decades has resulted in a large number of reactions that can now be performed successfully in an aqueous medium. Among these reactions are allylation reactions², the aldol condensation³, the Michael addition⁴, the Mannich reaction⁵, indium-mediated allylation and Grignard-type additions⁶ and the benzoin condensation⁷. Surprisingly, also notoriously solvent-insensitive reactions such as the Claisen rearrangement, the 1,3-dipolar cycloaddition and particularly the Diels-Alder reaction can benefit dramatically from an aqueous medium. Accelerations of the latter reaction in the order of 12,800 times have been achieved, simply by changing the solvent to water. The origins of this astonishing effect will be elucidated in Section 1.4. A more detailed overview of synthetic organic chemistry in water is given in two recent review articles by Lubineau⁸ and Li⁹ and in recent textbooks by Grieco¹⁰ and Li¹¹.

Apart from using an environmentally friendly solvent, it is also important to clean up the chemical reactions themselves by reducing the number and amount of side-products formed. For this purpose catalysts are a versatile tool. Catalysts have been used for thousands of years in processes such as fermentation and their importance has grown ever since. In synthetic organic chemistry, catalysts have found wide applications. In the majority of these catalytic processes, organic solvents are used, but also here the use of water is becoming increasingly popular¹².

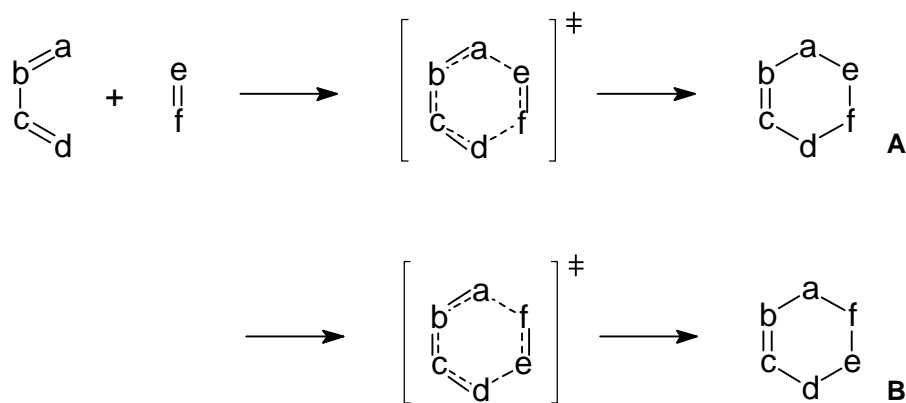
Also in industry, water is slowly gaining ground as is illustrated by the Ruhr Chemie Rhone-Poulenc hydroformylation process¹³. In this process in the years following 1984, 300,000 tons of propene have been converted annually into butanal using a highly water-soluble rhodium catalyst¹⁴. The extremely high solubility of the catalyst in water has been achieved through sulfonation of the triphenylphosphine ligands. Following this approach, many more water-soluble compounds have been prepared that can act as ligands for metal-catalysed transformations such as hydrogenations and hydroformylations^{14b,15}.

This thesis contributes to the knowledge of catalysis in water, as it describes an explorative journey in the, at the start of the research, untrodden field of catalysis of Diels-Alder reactions in aqueous media. The discussion will touch on organic chemistry, coordination chemistry and colloid chemistry, largely depending upon the physical-organic approach of structural variation for the elucidation of the underlying mechanisms and principles of the observed phenomena.

The remainder of this chapter will provide the necessary background, from which the incentive of catalysing Diels-Alder reactions in water and the aims of the study will become apparent.

1.2 The Diels-Alder reaction

In the Diels-Alder reaction (in older literature referred to as the “diene synthesis”) a six-membered ring is formed through fusion of a four- π component, usually a *diene* and a two- π component, which is commonly referred to as the *dienophile* (Scheme 1.1).



Scheme 1.1. Schematic representation of the Diels-Alder reaction. The versatility of the reaction is illustrated by the fact that heteroatoms are allowed at any of the positions a-f. Structures A and B indicate two regioisomeric products.

The Diels-Alder reaction has proven to be of great synthetic value, forming a key-step in the construction of compounds containing six-membered rings. The reaction is stereospecific in the sense that conformations of the reacting double bonds are fully retained in the configuration of the product. In this way, six new stereocentres can be formed in a single reaction step. The absolute configuration of the two newly formed asymmetric centres can be controlled efficiently (see Chapter 3).

1.2.1 History

The reaction is named after Otto Diels and Kurt Alder, two German chemists who studied the synthetic and theoretical aspects of this reaction in great detail. Their efforts have been rewarded with the 1950 Nobel prize. Contrary to what is usually assumed, they did not discover this reaction. The first example of a Diels-Alder reaction (the dimerisation of tetrachlorocyclopenta-dienone) stems from 1892¹⁶. The first chemist to identify the importance of the reaction was von Euler in 1920¹⁷, eight years before the famous paper by Diels and Alder appeared¹⁸. However, von Euler refrained from further exploring the reaction, since he, together with Haden, was already in the process of winning the 1929 Nobel prize on fermentative enzymes and the fermentation of sugars. Following the explorative work of Diels, Alder and co-workers, the Diels-Alder reaction became an important tool in synthetic organic chemistry.

An extremely readable historic account describing in more detail the chemistry and the chemists involved in the discovery of Diels-Alder reaction has been published recently by Berson¹⁹.

1.2.2 Mechanistic aspects²⁰

The Diels-Alder reactants as shown in Scheme 1.1 can consist of only hydrocarbon fragments (*homo-Diels-Alder reaction*) but can also contain one or more heteroatoms on any of the positions

a-f (*hetero Diels-Alder reaction*) leading to heterocyclic ring systems. The fact that many different combinations of carbon and hetero atoms are allowed demonstrates the enormous versatility of this reaction²¹.

Diels-Alder reactions can be divided into *normal electron demand* and *inverse electron demand* additions. This distinction is based on the way the rate of the reaction responds to the introduction of electron withdrawing and electron donating substituents. Normal electron demand Diels-Alder reactions are promoted by electron donating substituents on the diene and electron withdrawing substituents on the dienophile. In contrast, inverse electron demand reactions are accelerated by electron withdrawing substituents on the diene and electron donating ones on the dienophile. There also exists an intermediate class, the neutral Diels-Alder reaction, that is accelerated by both electron withdrawing and donating substituents.

The way the substituents affect the rate of the reaction can be rationalised with the aid of the *Frontier Molecular Orbital (FMO) theory*. This theory was developed during a study of the role of orbital symmetry in pericyclic reactions by Woodward and Hoffmann²² and, independently, by Fukui²³. Later, Houk contributed significantly to the understanding of the reactivity and selectivity of these processes²⁴.

The FMO theory states that a reaction between two compounds is controlled by the efficiency with which the molecular orbitals of the individual reaction partners interact. The interaction is most efficient for those orbitals that overlap best and are closest in energy. The FMO theory further assumes that the reactivity is completely determined by interactions of the electrons that are highest in energy of one of the reaction partners (i.e. those in the Highest Occupied Molecular Orbital, the HOMO) with the Lowest Unoccupied Molecular Orbital (LUMO) of the other partner. Applied to the Diels-Alder reactions, two modes of interaction are possible: the reaction can be controlled by the interaction of the HOMO of the diene and the LUMO of the dienophile (normal electron demand), or by the interaction between the LUMO of the diene and the HOMO of the dienophile (inverse electron demand), as illustrated in Figure 1.1. In the former case, a reduction of the diene-HOMO dienophile-LUMO energy gap can be realised by either raising the energy of the HOMO of the diene by introducing electron donating substituents or lowering the energy of the dienophile-LUMO by the introduction of electron withdrawing substituents. A glance at Figure 1.1 confirms that in the formation of two new σ -bonds, orbital symmetry is conserved so that, according to Woodward and Hoffmann, the reaction is *concerted*. In other words, no intermediate is involved in pericyclic processes such as the Diels-Alder reaction²⁵. This conclusion is consistent with a number of experimental observations: (a) The *cis* or *trans* conformation of the dienophile is fully conserved in the configuration of the cycloadduct, which proves that there is no intermediate involved with a lifetime long enough to allow rotation around a C-C bond. (b) The Hammett ρ -values, which can be considered as a measure of the development of charge in the activation process, are much smaller than those obtained for reactions known to proceed through charged intermediates. (c) Solvent effects on the Diels-Alder reaction are usually small or modest (see Section 1.2.3), excluding the

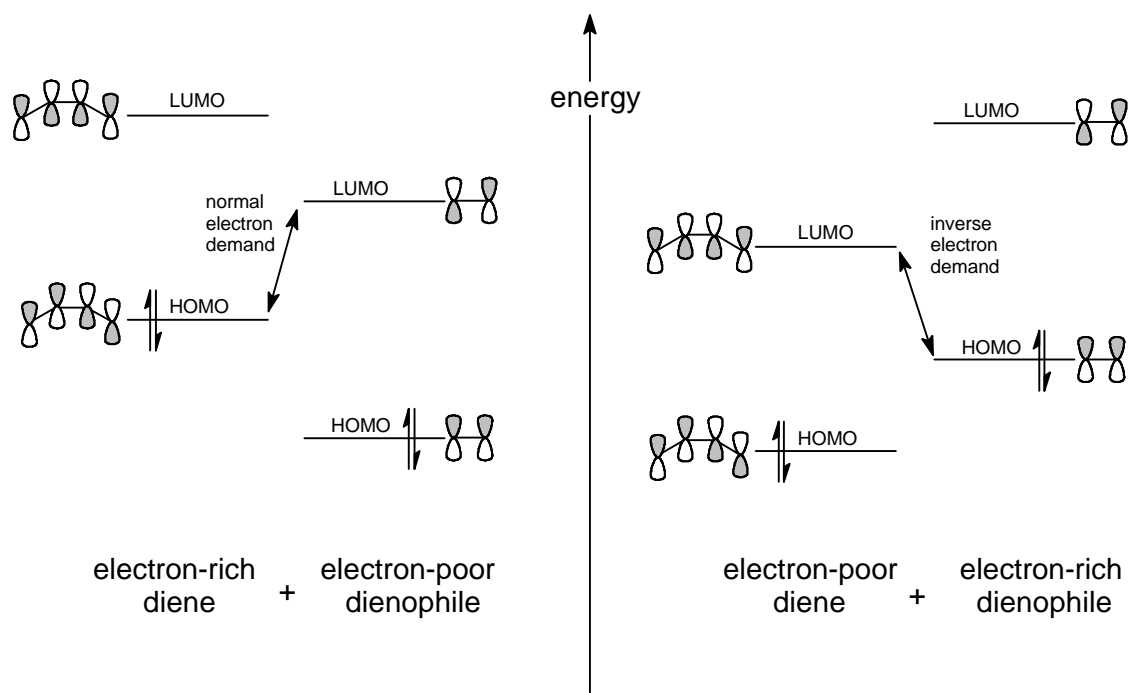
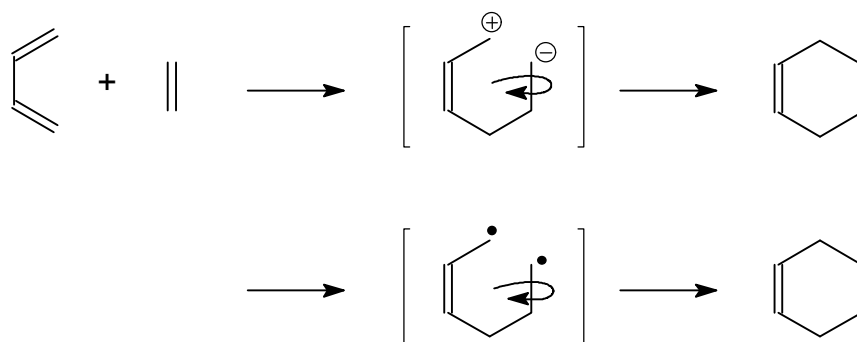


Figure 1.1. Orbital correlation diagram illustrating the distinction between normal electron demand (left side) and inverse electron demand (right side) Diels-Alder reactions.

involvement of charged intermediates in the rate determining step. (d) The magnitudes of volumes and entropies of activation are in line with two new σ -bonds being formed simultaneously²⁶. Also a large number of computer simulations are consistent with a concerted mechanism²⁷.

Despite this overwhelming body of evidence, two-step mechanisms have been suggested for the Diels-Alder reaction, probably inspired by special cases, where highly substituted dienes and/or dienophiles have been found to react through zwitterionic²⁸ or biradical²⁹ intermediates (Scheme 1.2).

In a recent experimental study of the femtosecond dynamics of a Diels-Alder reaction in the gas phase it has been suggested that both concerted and stepwise trajectories are present simultaneously³⁰. It is interesting to read the heated debates between Houk^{27,31} and Dewar³² on the



Scheme 1.2. Schematical representation of a zwitterionic and a biradical pathway of a Diels-Alder reaction.

concertedness of the Diels-Alder reaction. After extensive calculations and accurate determination of deuterium³³ and ¹⁴C³⁴ kinetic isotope effects and comparison with calculated values for the concerted and the step-wise pathway³⁵, a consensus has been reached in favour of the concerted mechanism.

The concertedness does not imply that in the activated complex the extent of formation of the two new σ -bonds is necessarily the same. Asymmetric substitution patterns on the diene and/or dienophile can lead to an *asynchronous* activation process³⁶. The extent of asynchronicity can be either assessed from kinetic isotope effects³⁷ or predicted from the FMO-coefficients of the terminal carbons of diene and dienophile. Qualitatively, the terminus with the highest FMO-coefficient can be identified using resonance theory. The magnitudes of these coefficients can be calculated³⁸.

The FMO coefficients also allow qualitative prediction of the kinetically controlled *regioselectivity*, which needs to be considered for asymmetric dienes in combination with asymmetric dienophiles (A and B in Scheme 1.1). There is a preference for formation of a σ -bond between the termini with the most extreme orbital coefficients³⁸.

Another form of selectivity can arise when substituted dienes and dienophiles are employed in the Diels-Alder reaction. Two different cycloadducts denoted as *endo* and *exo* can then be formed (Figure 1.2).

Under the usual conditions their ratio is kinetically controlled. Alder and Stein already discerned that there usually exists a preference for formation of the *endo* isomer (formulated as a tendency of maximum accumulation of unsaturation, the Alder-Stein rule)³⁹. Indeed, there are only very few examples of Diels-Alder reactions where the *exo* isomer is the major product⁴⁰. The interactions underlying this behaviour have been subject of intensive research. Since the reactions leading to *endo* and *exo* product share the same initial state, the differences between the respective transition-state energies fully account for the observed selectivity. These differences are typically in the range of 10-15 kJ per mole⁴¹.

Woodward and Katz⁴² suggested that secondary orbital interactions are of primary importance. These interactions are illustrated in Figure 1.2 for the normal electron demand (HOMO diene-LUMO dienophile controlled) Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone. The symmetry allowed overlap between π -orbitals of the carbonyl group of the dienophile and the diene-HOMO is only possible in the *endo* activated complex. Hence, only the *endo* transition state is stabilised so that the reaction forming the *endo* adduct is faster than that yielding *exo* product.

Interestingly *endo* selectivity is observed even in reactions of dienophiles bearing substituents without π -orbitals⁴³. For example, the *endo* preference of Diels-Alder reactions of cyclopropene has been rationalised on the basis of a special type of secondary orbital interactions⁴⁴. This interpretation has been criticised by Mellor, who attributed the *endo* selectivity to steric interactions⁴⁵. Steric effects are frequently suggested as important in determining the selectivity of Diels-Alder reactions, particularly of α -substituted dienophiles, and may ultimately lead to *exo*-selectivity^{40a,46}. For other systems, steric effects in the *exo* activated complex, can enhance *endo* selectivity^{43,47}. Also London-

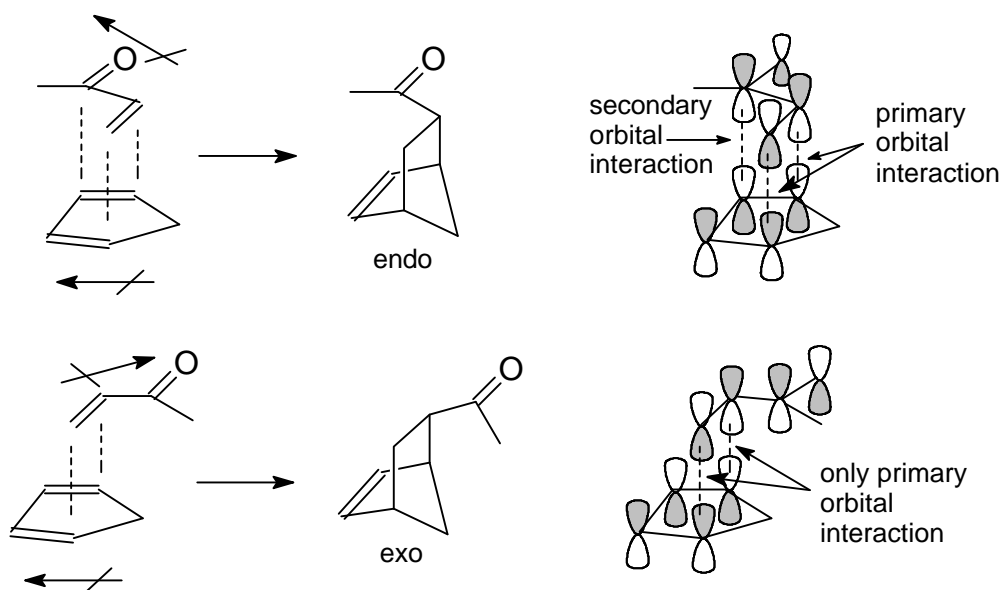


Figure 1.2. Endo and exo pathway for the Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone. As was first noticed by Berson, the polarity of the endo activated complex exceeds that of the exo counterpart due to alignment of the dipole moments of the diene and the dienophile⁸¹. The symmetry-allowed secondary orbital interaction that is only possible in the endo activated complex is usually invoked as an explanation for the preference for endo adduct exhibited by most Diels-Alder reactions.

dispersion interactions have been considered. It has been argued that these interactions can sometimes override secondary orbital interactions⁴⁸.

Theoretical work by the groups directed by Sustmann⁴⁹ and, very recently, Mattay⁵⁰ attributes the preference for the formation of endo cycloadduct in solution to the polarity of the solvent. Their calculations indicate that in the gas phase the exo transition state has a lower energy than the endo counterpart and it is only upon introduction of the solvent that this situation reverses, due to the difference in polarity of both transition states (Figure 1.2). Mattay⁵⁰ stresses the importance of the dienophile transoid-cisoid conformational equilibrium in determining the endo-exo selectivity. The transoid conformation is favoured in solution and is shown to lead to endo product, whereas the cisoid conformation, that is favoured in the gas phase, produces the exo adduct. This view is in conflict with ab initio calculations by Houk, indicating an enhanced secondary orbital interaction in the cisoid endo transition state⁵¹.

In summary, it seems that for most Diels-Alder reactions secondary orbital interactions afford a satisfactory rationalisation of the endo-exo selectivity. However, since the endo-exo ratio is determined by small differences in transition state energies, the influence of other interactions, most often steric in origin and different for each particular reaction, is likely to be felt. The compact character of the Diels-Alder activated complex (the activation volume of the retro Diels-Alder reaction is negative) will attenuate these effects⁵². The ideas of Sustmann⁴⁹ and Mattay⁵⁰ provide an attractive alternative explanation, but, at the moment, lack the proper experimental foundation.

1.2.3 Solvent effects on Diels-Alder reactions⁵³

Solvents exert their influence on organic reactions through a complicated mixture of all possible types of noncovalent interactions. Chemists have tried to unravel this entanglement and, ideally, want to assess the relative importance of all interactions separately. In a typical approach, a property of a reaction (e.g. its rate or selectivity) is measured in a large number of different solvents. All these solvents have unique characteristics, quantified by their physical properties (i.e. refractive index, dielectric constant) or empirical parameters (e.g. $E_T(30)$ -value, AN). Linear correlations between a reaction property and one or more of these solvent properties (Linear Free Energy Relationships - LFER) reveal which noncovalent interactions are of major importance. The major drawback of this approach lies in the fact that the solvent parameters are often not independent. Alternatively, theoretical models and computer simulations can provide valuable information. Both methods have been applied successfully in studies of the solvent effects on Diels-Alder reactions.

1.2.3a Solvent effects on the rate of Diels-Alder reactions

Many textbooks, when discussing solvent effects on organic reactions, refer to the Diels-Alder cycloaddition as a typical example of a reaction that is indifferent towards the choice of the solvent. This feature is exemplified by the data in Table 1.1, referring to the rate of dimerisation of cyclopentadiene. For this reaction, the second-order rate constants in a broad range of organic solvents are similar to each other and even to the rate constant in the absence of solvent. The data in Table 1.1 refer to the very special case of a Diels-Alder reaction between two purely hydrocarbon reactants. Normally, Diels-Alder reactions only proceed at an appreciable rate when either diene or dienophile is activated by an electron donating or withdrawing substituent. These substituents almost invariably contain heteroatoms. These atoms interact efficiently with the solvent, resulting in an amplification of the solvent effect on the reaction. A multitude of these processes have been studied. The first correlation of the rate of Diels-Alder reactions with solvent parameters was published in 1974⁵⁴. Relatively poor correlations of the rate of several common Diels-Alder reactions with the Brownstein polarity parameter S were obtained. Schneider and Sangwan correlated the rate of some Diels-Alder reactions in aqueous mixtures with the solvophobicity parameter Sp ⁵⁵. Some of their data have been criticised by Blokzijl⁵⁶. More thorough analyses of solvent effects on Diels-Alder reactions have been reported by the groups of Desimoni and Mayoral.

Desimoni et al. initially advocated the Acceptor Number (AN) as the dominant solvent parameter⁵⁷. The AN describes the ease with which a solvent can act as an electron pair acceptor (Lewis acid) and is dominated by hard-hard interactions⁵⁸. Desimoni et al.⁵⁷ usually obtained hyperbolic correlations between the logarithm of the second-order rate constant and the AN. Further investigation revealed Diels-Alder reactions for which the rate constants did not yield satisfactory correlations with the AN. These examples included either reactions that were next to insensitive to solvent effects (like the

Table 1.1. Second-order rate constants k_2 for the dimerisation of cyclopentadiene in solution and in the gas phase at 25°C^a.

solvent / state	k_2 (M ⁻¹ s ⁻¹)
gas phase	$6.9 \cdot 10^{-7}$
neat	$5.6 \cdot 10^{-7}$
carbontetrachloride	$7.9 \cdot 10^{-7}$
nitrobenzene	$13 \cdot 10^{-7}$
ethanol	$19 \cdot 10^{-7}$

^a Data taken from ref. 61.

dimerisation of cyclopentadiene - Table 1.1) or reactions that responded mainly to the electron-pair-donor character of the solvent⁵⁹. These observations prompted the authors to divide Diels-Alder reactions into three categories. In type A, the rate constants increase with increasing Lewis-acidic character of the solvent quantified by the AN . This behaviour reflects $LUMO_{\text{solvent}}-HOMO_{\text{solute}}$ interactions and is similar to Lewis-acid catalysis (see Section 1.2.4) In type B, electron donation by the solvent through soft-soft interactions, quantified by the $D\pi$ parameter⁶⁰, retards the reaction. $HOMO_{\text{solvent}}-LUMO_{\text{solute}}$ interactions are held responsible for this observation. Unfortunately the role of hydrogen-bond donor solvents has not been investigated for this class of reactions, partly due to experimental problems. Diels-Alder reactions belonging to type C show very small solvent effects and are relatively insensitive to specific solute-solvent interactions. Solvent-solvent interactions are then dominant, resulting in a correlation with the cohesive energy (d_H^2) of the solvent. The dimerisation of cyclopentadiene is a typical example (Table 1.1). Another example will be encountered in Section 1.4.1. Unfortunately, in none of the report produced by the Desimoni-group is water included among the solvents.

Studies by the group directed by Mayoral have been limited to Diels-Alder reactions of type A. When water was not included, the rate constants correlate with the solvent hydrogen-bond-donating capacity α ⁶². Upon inclusion of water the solvophobicity parameter, Sp , contributed significantly in the LFER⁶³. When only mixtures of water with acetone⁶⁴, 1,4-dioxane⁶⁴ or hexafluoroisopropanol⁶⁵ were considered, the Sp parameter sufficed for describing the solvent effect.

Recently the solvent effect on the [4+2] cycloaddition of singlet oxygen to cyclic dienes has been subjected to a multiparameter analysis. A pre-equilibrium with charge-transfer character is involved, which is affected by the solvent through dipolarity-polarisability (p^*) and solvophobic interactions (d_H and Sp)⁶⁶. Another multiparameter analysis has been published by Gajewski, demonstrating the importance of the cohesive energy density and, again, the α -parameter in the solvent effect on an A-type Diels-Alder reaction⁶⁷.

Firestone et al.⁶⁸ demonstrated the importance of solvent density in the special case of intramolecular Diels-Alder reaction in highly viscous media. Efficient packing of the hydrocarbon solvent was

assumed to impede translational motion of the solute, which facilitates the cycloaddition.

In 1990 Grieco et al. introduced an interesting new medium for the Diels-Alder reaction: a 5 molar solution of lithium perchlorate in diethyl ether⁶⁹. Grieco⁶⁹ and later also Kumar⁷⁰ attributed the appreciable accelerations of Diels-Alder reactions in this medium to a high internal pressure. This view has been criticised and, as alternative explanations, Lewis-acid catalysis by the lithium cation has been suggested⁷¹, as well as efficient stabilisation of the Diels-Alder transition state by this highly polar medium⁷². Faita et al. have pointed out that only when Diels-Alder reactions are not sensitive to Lewis-acid catalysis, internal pressure can explain the, in that case always modest, accelerations⁷³. In contrast, the large accelerations commonly observed should be attributed to the lithium ion acting as a Lewis acid. An assessment of the Lewis acidity of this ion in organic media has been published recently⁷⁴. Desimoni et al. have performed a kinetic study on the effect of lithium perchlorate and other perchlorates in different organic solvents⁷⁵. From a synthetic point of view solutions of lithium perchlorate in dichloromethane⁷⁶ and nitromethane⁷⁷ further improve the efficiency. A major drawback of all these perchlorate containing media is their potentially explosive character. A safe alternative has recently been provided by Grieco in the form of lithium trifluoromethanesulfonimide in acetone or diethylether⁷⁸.

In summary, solvents can influence Diels-Alder reactions through a multitude of different interactions, of which the contributions to the overall rate uniquely depend on the particular solvent-diene-dienophile combination. Scientists usually feel uncomfortable about such a situation and try to extract generalities. When limited to the most extensively studied type A Diels-Alder reactions this approach seems feasible. These Diels-Alder reactions are dominated by hydrogen bonding interactions in combination with solvophobic interactions. This observation predicts a very special role of water as a solvent for type A Diels-Alder reactions, which is described in Section 1.4.

1.2.3b The effects of solvents on the selectivity of Diels-Alder reactions.

The influence of the solvent on the *regioselectivity* is perfectly described by the FMO theory⁷⁹. As mentioned in Section 1.2, the regioselectivity is determined by the orbital coefficients on the terminal carbons of diene and dienophile which, in turn, are determined by the electronic influences of the substituents. The influence of substituents can be modified through electron donation or withdrawal by the solvent. The latter can be achieved efficiently through hydrogen bonding interactions, as has become apparent from multiparameter analyses of the solvent effect on regioselectivity, which have invariably revealed a dominant contribution of the hydrogen bond-donating character of the solvent (α)^{65,80}.

In 1961 Berson et al. were the first to study systematically the effect of the solvent on the *endo-exo selectivity* of the Diels-Alder reaction⁸¹. They interpreted the solvent dependence of the *endo-exo* ratio by considering the different polarities of the individual activated complexes involved. The *endo* activated complex is of higher polarity than the *exo* activated complex, because in the former the dipole moments of diene and dienophile are aligned, whereas in the latter they are pointing in

opposite directions (see Figure 1.2). Hence, polar solvents attenuate the preference for the formation of endo cycloadduct. Berson et al. actually based an empirical solvent polarity scale on the selectivity of the Diels-Alder reaction between cyclopentadiene and methyl acrylate: $\Omega = \log(\text{endo/exo})$. The importance of solvent polarity has also been discerned by other authors on the basis of experimental⁷⁹ and theoretical work^{49,50}. Interestingly, a group of Japanese researchers has observed a correlation between the endo-exo ratio and solvent polarisability⁸². Extensive multiparameter analyses by the group directed by Mayoral demonstrated that a proper description of the solvent effect on the endo-exo ratio requires a number of different interactions^{62,63a,65,80}. Hydrogen bonding by the solvent (quantified by α) contributes most significantly, but also solvent polarity (quantified by p^* or E_T^N) and solvent solvophobicity (quantified by Sp) are important^{53c}. Interestingly, when only aqueous mixtures are considered, the endo-exo ratios exhibit a satisfactory correlation with the Sp parameter^{64,83}.

The solvent effect on the *diastereofacial selectivity* in the reactions between cyclopentadiene and (1R,2S,5R)-menthyl acrylate is dominated by the hydrogen bond donor characteristics of the solvent together with its polarity as expressed by E_T^N and p^* ^{62,65}.

In 1990 Grieco introduced a 5 molar solution of lithium perchlorate as a new medium for the Diels-Alder reaction that is capable of inducing not only an improvement of the rate but also of the endo-exo⁶⁹ and diastereofacial⁸⁴ selectivity. Grieco recently used lithium trifluoromethanesulfon-imide in acetone or diethylether as a nonexplosive alternative to the perchlorate solution. Interestingly, this medium seems to favour the formation of the exo-adduct⁷⁸. An explanation for this pattern has not yet been provided.

1.2.4 Lewis-acid catalysis of Diels-Alder reactions

Under normal conditions only combinations of dienes and dienophiles that have FMO's of similar energy can be transformed into a Diels-Alder adduct. When the gap between the FMO's is large, forcing conditions are required, and undesired side reactions and retro Diels-Alder reactions can easily take over. These cases challenge the creativity of the organic chemist and have led to the invention of a number of methods for promoting reluctant Diels-Alder reactions under mild conditions⁸⁵. One very general approach, performing Diels-Alder reactions under high pressure, makes use of the large negative volume of activation (about -25 to -45 cm³ per mole) characteristic for this reaction. The rate enhancements are modest, typically in the order of a factor 10 at a pressure of 1500 atm²⁶. Selectivities also benefit from an increase in pressure²⁶. Another physical method uses ultrasound irradiation. However, the observed accelerations are invariably a result of indirect effects such as the development of low concentrations of catalytically active species and more efficient mixing of the heterogeneous reaction mixtures under ultrasound conditions⁸⁶. Catalysis of Diels-Alder reactions through formation of supramolecular assemblies is becoming increasingly popular. Large molecules containing a cavity (e.g. cyclodextrins^{55,83,87} or related

basket⁸⁸ or capsule-like⁸⁹ structures) can bind both Diels-Alder reagents simultaneously and promote their reaction. The same principle accounts for catalysis by antibodies⁹⁰ and enzymes⁹¹. Also heterogeneous systems such as clays⁹², alumina⁹³ or silica gels⁹⁴ and even microporous organic crystals⁹⁵ have catalytic potential. Finally, catalysis by Brønsted acids⁹⁶, Brønsted bases⁹⁷ and radicals⁹⁸ has found application in some special Diels-Alder reactions.

By far the most effective method, however, is catalysis by Lewis-acids. In organic solvents, accelerations of the order of 10^4 to 10^6 , accompanied by a considerable increase in selectivity, are no exception. The remarkable effects that Lewis acids exert on the rate of Diels-Alder reactions were discovered by Yates and Eaton in 1960⁹⁹. They studied the reaction between maleic anhydride and anthracene in the presence of aluminium trichloride, which was complete in 1.5 minutes, whereas they estimated the required reaction time under the same conditions in the absence of the catalyst to be approximately 4800 hours ! The effect of Lewis acids on the selectivity was first demonstrated by Sauer and Kredel six years later¹⁰⁰. Upon addition of $\text{AlCl}_3 \cdot \text{OEt}_2$ the endo-exo selectivity of the reaction between cyclopentadiene and methyl acrylate improved from 82% to 98% endo. Also the regioselectivity¹⁰¹ and the diastereofacial selectivity¹⁰² increased in the presence of Lewis acids.

The beneficial effects of Lewis acids are limited to reagents containing Lewis-basic sites close to the reaction centre. Fortunately, in nearly all Diels-Alder reactions one of the reagents, most frequently the dienophile, meets this requirement. Coordination takes place to a lone pair on one of the reactants and, hence, has a $\eta^1 \sigma$ -character¹⁰³. The mechanism of activation by Lewis acids can be understood with the aid of the FMO theory. The electron withdrawing character of the catalyst lowers the energy of the LUMO of the reactant to which it is coordinated, resulting in a decrease of the HOMO-LUMO energy difference and, in turn, an increase in the rate of the Diels-Alder reaction. The effects of Lewis-acids on selectivity can be understood by considering one of the simplest dienophile-Lewis acid complexes: protonated acrolein¹⁰⁴. Figure 1.3 illustrates the redistribution of electron density and lowering of FMO energy that takes place upon coordination.

The regioselectivity benefits from the increased polarisation of the alkene moiety, reflected in the increased difference in the orbital coefficients on carbon 1 and 2. The increase in endo-exo selectivity is a result of an increased secondary orbital interaction that can be attributed to the increased orbital coefficient on the carbonyl carbon^{38,105}. Also increased dipolar interactions, as a result of an increased polarisation, will contribute³⁸. Interestingly, Yamamoto has demonstrated that by using a very bulky catalyst the endo-pathway can be blocked and an excess of exo product can be obtained¹⁰⁶. The increased diastereofacial selectivity has been attributed to a more compact transition state for the catalysed reaction as a result of more efficient primary and secondary orbital interactions¹⁰⁴ as well as conformational changes in the complexed dienophile^{51,107}. Calculations show that, with the polarisation of the dienophile, the extent of asynchronicity in the activated complex increases^{38,108}. Some authors even report a zwitterionic character of the activated complex of the Lewis-acid catalysed reaction^{105,109}. Currently, Lewis-acid catalysis of Diels-Alder reactions is everyday practice in synthetic organic chemistry.

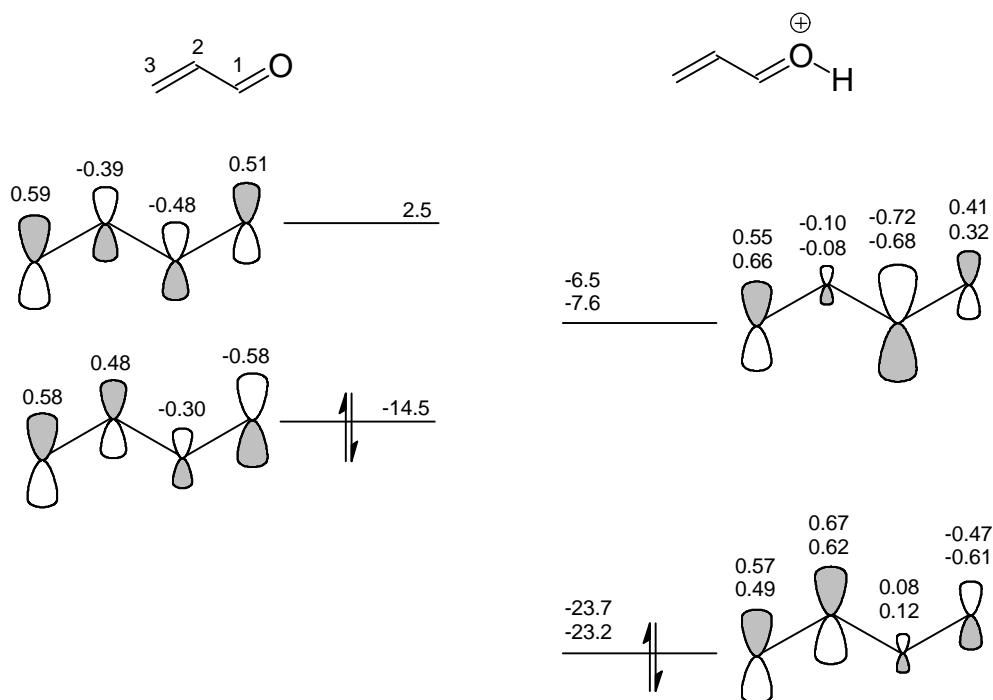


Figure 1.3. Frontier orbital energies (eV) and coefficients for acrolein and protonated acrolein. In the latter case the upper numbers refer to the situation where bond lengths and angles correspond to those of acrolein. The lower numbers are more suitable for a hydroxyallyl cation. The actual situation is assumed to be intermediate. The data are taken from ref. 104.

Unfortunately, the number of mechanistic studies in this field stands in no proportion to its versatility^{53b}. Thermodynamic analysis revealed that the beneficial effect of Lewis-acids on the rate of the Diels-Alder reaction can be primarily ascribed to a reduction of the enthalpy of activation ($\Delta\Delta H^\ddagger = 30\text{-}50$ kJ/mole) leaving the activation entropy essentially unchanged ($T\Delta\Delta S^\ddagger = 0\text{-}10$ kJ/mol)^{53b,110}. Solvent effects on Lewis-acid catalysed Diels-Alder reactions have received very little attention. A change in solvent affects mainly the coordination step rather than the actual Diels-Alder reaction. Donating solvents severely impede catalysis^{53b}. This observation justifies the widespread use of inert solvents such as dichloromethane and chloroform for synthetic applications of Lewis-acid catalysed Diels-Alder reactions.

1.3 Water and hydrophobic effects

Aristotle recognised the importance of water by including it among the four elements along with fire, earth and air. In its many different functions, water is essential to the earth as we know it. Life critically depends on the presence of water. It is the medium of cells and is essential for the structure of proteins, cell membranes and DNA¹¹¹. It has been estimated that more than 99 % of the molecules in the human body are actually water molecules¹¹².

Despite its very simple molecular structure, many characteristics of water are still poorly understood

and fundamental studies continue to be published¹¹³. Perhaps the most intriguing property of water is the occurrence of hydrophobic effects¹¹⁴. These effects are 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), molecular recognition phenomena¹¹⁵ and surface forces¹¹⁶. Likewise, industrial processes can depend critically on hydrophobic effects¹¹⁷.

Hydrophobic effects include two distinct processes: hydrophobic hydration and hydrophobic interaction. Hydrophobic hydration denotes the way in which nonpolar solutes affect the organisation of the water molecules in their immediate vicinity. The hydrophobic interaction describes the tendency of nonpolar molecules or parts thereof to stick together in aqueous media^{114d}. A related frequently encountered term is “hydrophobicity”. This term is essentially not correct since overall attractive interactions exist between water and compounds commonly referred to as “hydrophobic”¹¹⁸. As Finney¹¹⁹ correctly pointed out, it is more correct to refer to these compounds as “nonpolar”. Following this line of argument, essentially also the terms “hydrophobic effect” and “hydrophobic interaction” are not correct. However, since they are commonly accepted, we will not refrain from using them in this thesis.

1.3.1 Hydrophobic hydration

The interest in hydrophobic hydration mainly stems from the peculiar thermodynamics connected with the transfer of nonpolar molecules from the gas phase to water as was originally noticed by Butler in 1937¹²⁰. At room temperature, the transfer is typically characterised by an unfavourable change in Gibbs energy. The enthalpy change is relatively small and usually favourable, leaving the entropy decrease to account for the positive ΔG^\ominus ¹²¹. Interestingly, for molecules with sizes in the range from hydrogen to cyclohexane, the Gibbs energy change is almost independent of the size of the solute molecules. The size does influence ΔH^\ominus and $T\Delta S^\ominus$ significantly, but to opposite extents so that they compensate each other in their influence on ΔG^\ominus ^{114d}.

With increasing temperature the enthalpy of hydration of nonpolar gasses increases rapidly, eventually becoming positive. This large positive change in heat capacity is characteristic for hydrophobic hydration. The enthalpy increase overshadows the entropy change becoming less unfavourable, so that the Gibbs energy of solvation is even more unfavourable at higher temperatures (see Figure 1.4). Interestingly, there exist universal temperatures where the hydration enthalpy and entropy pass through zero, irrespective of the solute. This pattern indicates that the enthalpy and entropy changes upon dissolution of nonpolar compounds are dominated by the properties of water.

The solvation thermodynamics have been interpreted in a classical study by Frank and Evans in terms of the iceberg model¹²². This model states that the water molecules around a nonpolar solute show an increased quasi-solid structuring. This pattern would account for the strongly negative

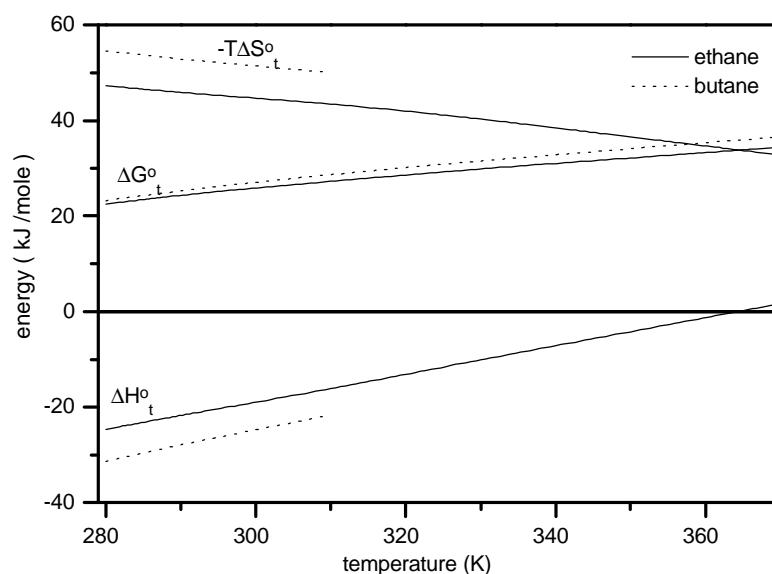


Figure 1.4. Temperature dependence of the change in Gibbs energy, enthalpy and entropy upon transfer of ethane and butane from the gas phase to water. The data refer to transfer from the vapour phase at 0.101 MPa to a hypothetical solution of unit mole fraction and are taken from ref. 125.

entropy change upon solvation. The authors supported their model by referring to the occurrence of solid clathrate hydrates¹²³. As to what their icebergs would actually look like, Frank and Evans state: “It is not implied that the structure is exactly ice-like, nor is it necessarily the same in every case where the word iceberg is used.”

In 1959, fourteen years after the appearance of the paper of Frank and Evans, Kauzmann stressed the importance of hydrophobic effects in protein folding¹²⁴. Interestingly, he pointed out that the hydrophobic hydration shell, the iceberg, cannot possibly have a solid character. He argued that dissolution of nonpolar compounds in water leads to a volume decrease, whereas the formation of solid-like hydration shells would be expected to lead to a volume increase. Remarkably, this observation did not stop Kauzmann from suggesting in the same article that the large heat capacity change might well be attributed to the melting of icebergs.

The ideas of Frank, Evans and Kauzmann had a profound influence on the way chemists thought about hydrophobic effects in the decades that followed. However, after the study of the hydrophobic hydration shell through computer simulations became feasible, the ideas about the hydrophobic hydration gradually changed. It became apparent that the hydrogen bonds in the hydrophobic hydration shell are *not*¹²⁶, or only to a minor extent¹²⁷, stronger than in normal water which is not compatible with an iceberg character of the hydration shell.

Recently, this observation has been confirmed experimentally through neutron scattering studies, making use of isotopic substitution¹²⁸. These studies have revealed that the water molecules in the

hydrophobic hydration shell remain essentially fully hydrogen bonded. For each water molecule in contact with the apolar solute one O-H bond is oriented parallel to the nonpolar surface; the other bond points into bulk water. The neutron diffraction studies revealed no indication of either significantly stronger or more hydrogen bonds per volume element in the hydrophobic hydration shell. The structuring of water was not found to extend far beyond the first hydration shell, contrary to what had been frequently observed in computer simulations¹²⁸.

Very recently the first x-ray study (EXAFS) has been performed on hydrophobic hydration¹²⁹.

NMR studies revealed a decreased mobility of the water molecules in the first hydration shell of tetraalkylammonium salts at room temperature¹³⁰. This behaviour might be attributed to the physical presence of the solutes, blocking one way of escape of the water molecules. At lower temperatures, however, the mobility of the water molecules *increases* with increasing concentration of tetraalkylammonium salt. As yet, there is no satisfactory molecular explanation for this behaviour¹³⁰. Analogously, the rotational correlation times of the water molecules in the hydrophobic hydration shell of *t*-butanol significantly exceed those of bulk water¹³¹. It might well be that the reduced number of hydrogen bonding possibilities in the vicinity of the solute causes the reduced rotational freedom.

Although articles still appear supporting the iceberg model¹³², compelling evidence has now accumulated against it, so that there is a need for an alternative molecular picture of hydrophobic hydration. Reasonable agreement has been reached on the origin of the enthalpic term in the hydration of nonpolar molecules. This term can be accounted for by the significant interaction between the large number of water molecules of the first hydration shell and the solute¹³³. What remains is a large unfavourable entropy term requires explanation.

As is suggested frequently¹³⁴, this term might well result from the restriction of the hydrogen bonding possibilities experienced by the water molecules in the first hydration shell. For each individual water molecule this is probably a relatively small effect, but due to the small size of the water molecules, a large number of them are entangled in the first hydration shell, so that the overall effect is appreciable. This theory is in perfect agreement with the observation that the entropy of hydration of a nonpolar molecule depends linearly on the number of water molecules in the first hydration shell¹³⁵.

Another interesting view has been published recently by Besseling and Lyklema¹³⁶. Using a lattice model for water these authors reproduced the hydration thermodynamics without the need to invoke special structures around nonpolar solutes. In their interpretation water is a “macroscopic network of molecules connected by hydrogen bonds, rather than as a collection of clusters of finite size.”¹³⁷ The peculiar hydration thermodynamics result from a subtle enhancement of the type of ordering that is intrinsically present in liquid water. An analogy is drawn between the swelling of a polymer network and the uptake of nonpolar compounds by water. In both cases there is no local structuring and no breaking of the polymer or water network, but only a restriction of the configurational freedom of the polymer or water molecules.

A comparable molecular picture emerges from a molecular dynamics simulation of the hydrogen-bond dynamics of DMSO-water mixtures by Luzar¹³⁸. He observed that the presence of DMSO reduced the hydrogen-bond dynamics. Assuming that fluctuations in the hydrogen-bond network are promoted by their cooperative character (“hydrogen bonds most frequently break during a process of switching allegiance, with a newly formed bond replacing the broken one”)¹³⁸ the likelihood of these fluctuations decreases in the presence of solutes that cannot participate in them. This behaviour will not show up in the hydration enthalpy, but might well be important in explaining the entropy decrease.

In an alternative view, the size of the water molecule is invoked in a description of the hydrophobic hydration. Due to the small size, the chances of creating a cavity sufficiently large to accommodate a solute molecule are small when compared to organic solvents. A hard sphere model, not allowing any orientational order, reproduces the experimental Gibbs energies of hydration¹³⁹. Unfortunately, the authors did not determine the entropy and enthalpy changes. Chiefly these parameters distinguish hydration from solvation in other solvents. Limited solubility is a characteristic by no means unique for water.

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

1.3.2 Hydrophobic interactions

In the traditional view hydrophobic interactions are assumed to be driven by the release of water molecules from the hydrophobic hydration shells upon the approach of one nonpolar solute to another. Although the ideas about the structure of the hydrophobic hydration shell have changed, this view is essentially unaltered.

In the ideas of Kauzmann¹²⁴, formation of a hydrophobic hydration shell was supposed to induce aggregation. However, the opposite is true. The reorganisation of water molecules around a nonpolar solute is believed to *aid* the dissolution process. In other words: if the water would not reorganise and form a hydrophobic hydration shell, hydrogen bonds would have to be sacrificed upon dissolution of the solute so that the solubility of nonpolar compounds in water would be even smaller. Note that the unfavourable Gibbs energy change would then be enthalpy- and not entropy-dominated. It follows that the formation of a hydrophobic hydration shell counteracts aggregation of the solute and changes hydrophobic interactions from enthalpy-driven into somewhat less efficient entropy-driven processes. Note that there is still a large driving force left for hydrophobic interactions.

Surprisingly, some authors claim that methane molecules have a smaller tendency to associate in

water than in the gas phase¹⁴⁰. This conclusion disagrees with the results from recent computer simulations that have revealed an appreciable tendency for aggregation¹⁴¹.

The distinction between pairwise and bulk hydrophobic interactions is often made, although some authors doubt the existence of an intrinsic difference between the two¹⁴². Pairwise hydrophobic interactions denote the interactions between two isolated nonpolar solutes in aqueous solution. They occur in the regime where no aggregation takes place, hence below the critical aggregation concentration or solubility limit of the particular solute. If any breakdown of the hydrophobic hydration shell occurs, it will be only transient.

Bulk hydrophobic interactions, on the other hand, apply to the regime above the critical aggregation concentration or solubility limit. The hydrophobic hydration shells are now broken down to a significant extent. Bulk hydrophobic interactions have been suggested to be a result of the avoidance of overlap of hydrophobic hydration shells. Above a certain critical concentration, the number of available water molecules is thought to be insufficient for the formation of independent hydrophobic hydration shells for all solute molecules. The water molecules are then forced to be part of two hydration shells simultaneously. This pattern is assumed to be incompatible with a fully hydrogen bonded state and, hence, leads to a sacrifice of hydrogen bonds. Through aggregation, the system avoids this unfavourable situation. If this theory is correct, hydration shells have to be quite extensive, since critical aggregation concentrations can be extremely low. This appears to be in contrast with the outcomes of the neutron scattering studies, which showed that hydration shells are relatively short-ranged^{128a,b}.

Alternatively, one might argue whether processes such as the sudden appearance of micelles upon increasing the solute concentration are not simply a special kind of phase separation that sets in after saturation of the solution. The only difference between aggregation and a normal phase separation is the fact that the separation process is arrested in an intermediate stage because the efficient interactions between the polar headgroups of the amphiphile and the surrounding water molecules prevent the aggregates from forming still larger structures. Phase separations are well known to pass through a colloidal state and set in when the entropy of mixing is insufficient to overcome the unfavourable change in Gibbs energy associated with solubilisation.

What distinguishes water from ordinary organic solvents and justifies the term hydrophobic interaction is the molecular origin of the effect, being entropy driven in pure water at room temperature and resulting primarily from the strong water-water interactions.

1.4 Special effects of water on Diels-Alder reactions

For a long time water was not a popular solvent for the Diels-Alder reaction. Before 1980 its use had been reported only incidentally. Diels and Alder themselves performed the reaction between furan and maleic acid in an aqueous medium in 1931¹⁴³, an experiment which was repeated by Woodward and Baer in 1948¹⁴⁴. These authors noticed a change in endo-exo selectivity when

comparing the reaction in water with ether. Also in two patents the Diels-Alder reaction is mentioned in connection with water¹⁴⁵. In 1973 Eggelte, de Koning and Huisman studied the reaction of maleic acid with furan in several solvents¹⁴⁶. These authors noticed, for the first time, a beneficial effect of water on the Diels-Alder reaction. Still, it was not until the work of Breslow that it became common knowledge that water was a unique medium for Diels-Alder reactions^{87a}.

1.4.1 The effect of water on the rate of Diels-Alder reactions

The extreme influence water can exert on the Diels-Alder reaction was rediscovered by Breslow in 1980, much by coincidence^{87a}. While studying the effect of β -cyclodextrin on the rate of a Diels-Alder reaction in water, accidentally, the addition of the cyclodextrin was omitted, but still rate constants were observed that were one to two orders of magnitude larger than those obtained in organic solvents. The investigations that followed this remarkable observation showed that the acceleration of Diels-Alder reactions by water is a general phenomenon. Table 1.2 contains a selection from the multitude of Diels-Alder reactions in aqueous media that have been studied. Note that the rate enhancements induced by water can amount up to a factor 12,800 compared to organic solvents (entry 1 in Table 1.2).

Breslow immediately grasped the significance of his observation. He interpreted this discovery in terms of a hydrophobic effect: "Since in the Diels-Alder reaction ... the transition state ... brings together two nonpolar groups, one might expect that in water this reaction could be accelerated by hydrophobic interactions"^{87a}.

Breslow supported this suggestion by demonstrating that the cycloaddition can be further accelerated by adding "anti chaotropic" salts such as lithium chloride, whereas "chaotropic" salts such as guanidium chloride led to a retardation^{87a,c,147}. On the basis of these experiments Breslow excluded all other possible explanations for the special effect of water on the Diels-Alder reaction¹⁴⁸.

Still numerous alternative explanations have been offered. Grieco, studying compounds of obvious amphiphilic character, suggested that micellar catalysis might underlie the high efficiency of his reactions in aqueous solution compared to organic solvents¹⁴⁹. For many of the reactions that have been studied by the Grieco group, this might well be correct^{149,150}. This suggestion inspired some authors to claim aggregation phenomena as general explanations for the aqueous acceleration of Diels-Alder reactions^{87b,151}. Also Breslow, through the occasional use of terms such as "hydrophobic packing"^{87c,147,152} and "aggregation"¹⁴⁸ seems to suggest that hydrophobic interactions induce pre-association of the reactants. Although it is likely that the lifetime of encounter complexes of nonpolar molecules in water exceeds that in organic solvents, this pre-association is definitely not extensive enough to be held responsible for the observed rate effects. This conclusion follows from vapour pressure measurements which indicate that cyclopentadiene at concentrations up to 40 mM follows Raoult's law. Hence, on average this compound is distributed homogeneously throughout the aqueous solution⁵⁶. Also kinetic measurements on the intramolecular Diels-Alder reaction of **1.4** (entry 2 in Table 1.2) support this idea. In this reaction diene and dienophile are already associated

and still water is capable of accelerating this process by a factor of 153 compared to reaction in *n*-hexane⁵⁶.

Alternatively, authors have repeatedly invoked the internal pressure of water as an explanation of the rate enhancements of Diels-Alder reactions in this solvent^{69,153}. They were probably inspired by the well known large effects of the external pressure^{26b,c} on rates of cycloadditions. However, the internal pressure of water is very low⁶¹ and offers no valid explanation for its effect on the Diels-Alder reaction. The internal pressure is defined as the energy required to bring about an infinitesimal change in the volume of the solvents at constant temperature: $p_i = (\partial E / \partial V)_T$ ¹⁵⁴. Due to the open and relatively flexible hydrogen-bond network of water, a small change in volume of this solvent does not require much energy. A related, but much more applicable solvent parameter is the cohesive energy density (*ced*). This quantity is a measure of the energy required for evaporation of the solvent per unit volume: $ced = (DH_{vap} - RT) / V_M$ ¹⁵⁴. In contrast to the internal pressure, the *ced* of water is extremely high, due to the large number of hydrogen bonds per unit

Table 1.2. Relative rate constants of some selected Diels-Alder reactions in water compared to organic solvents of different hydrogen bond donor capacities.

		Aprotic	EtOH	HFP ^a	H ₂ O
1 ^b		1 (hexane)	28.0	4320	12800
2 ^c		1 (hexane)	1.90	-	153
3 ^b		1 (CH ₃ CN)	4.79	100	290
		1 (CH ₃ CN)	2.49	22.6	71.0
4 ^d		1 (hexane)	-	180	138
5 ^e		a 1 (CH ₃ CN)	1.69	-	8.95
		b -	1	-	102
6 ^f		1 (toluene)	1.14	5.49	44.3

^a 1,1,1,3,3,3-hexafluoropropanol ^b Taken from ref.157 and 166b ^c Taken from ref. 56 ^d Taken from ref. 158 and 166c ^e Taken from ref. 159 and 166c ^f Taken from ref. 160 and 166c

volume. When describing dissolution processes, the *ced* of the solvent is much more relevant than its internal pressure, since the creation of a cavity to accommodate the solute normally leads to the rupture of solvent-solvent interactions (related to the enthalpy of evaporation) and not to some infinitesimal change of solvent-solvent distances. The *ced* essentially quantifies solvophobicity, and as such, it has been successfully used by Gajewski in a multiparameter equation describing the

solvent effect on a Diels-Alder reaction where one of the solvents was water⁶⁷. The importance of the *ced* (alongside the hydrogen-bond donating capacity) in this study underlines the importance of hydrophobic interactions in rationalising the effect of water on Diels-Alder reactions. Blokzijl introduced the “enforced hydrophobic interactions” to describe the activation of Diels-Alder reactions in water. The term “enforced” is used to stress the fact that the association of the nonpolar reagents is driven by the reaction and only enhanced by water¹⁵⁵.

The importance of hydrophobic interactions in the aqueous acceleration is further demonstrated by a qualitative study described by Jenner on the effect of pressure on Diels-Alder reactions in water and a number of organic solvents¹⁵⁶. Invariably, the reactions in water were less accelerated by pressure than those in organic solvents, which is in line with the notion that pressure diminishes hydrophobic interactions.

Studies of solvent effects on type A Diels-Alder reactions by a large number of authors, as described in Section 1.2.3a, revealed that reactivity was primarily determined by two solvent parameters: the hydrogen-bond donating capacity and the solvophobicity. This pattern strongly suggests that in water, a hydrogen bond donating solvent *par excellence*, the Diels-Alder benefits not only from hydrophobic interactions but also from hydrogen-bonding interactions. The small size of water molecules allows efficient interaction with hydrogen-bond acceptors by forming more hydrogen bonds than protic organic solvents⁵⁰. This suggestion is supported by detailed kinetic studies on a number of carefully selected Diels-Alder reactions. In entry 3 of Table 1.2 the reactions of cyclopentadiene with a carbonyl- (**1.6**) and a sulfonyl- (**1.8**) activated dienophile are compared. Due to the insulating effect of the sulfur atom in **1.8**, the reactivity of this compound is much less affected by hydrogen bonding than the reactivity of **1.6**¹⁵⁷. This decreased sensitivity of **1.8** to hydrogen bonding shows up in a much less pronounced water-induced acceleration as compared to **1.6**¹⁵⁷. Further proof for the importance of hydrogen-bonding interactions came from the work of Wijnen, who showed that water also accelerated the retro Diels-Alder reaction (entry 4)¹⁵⁸. Retro Diels-Alder reactions are characterised by much smaller activation volumes than the bimolecular reaction. Hence, it was assumed that hydrophobic interactions are of little influence in this process. Nevertheless impressive rate enhancements have been observed, which have been ascribed to hydrogen bonding interactions. The large rate constant in the strongly hydrogen-bond donating solvent 1,1,1,3,3,3-hexafluoropropanol (HFP) strongly supports this view¹⁵⁸. In another approach, van der Wel and Wijnen selected a Diels-Alder reaction where the reactants lack hydrogen-bond accepting sites (entry 5)¹⁵⁹. The acceleration of the reaction of **1.12a** with **1.2** by water was modest, as was expected in the absence of activation by hydrogen bonds. Moreover, upon introduction of a hydrogen-bond accepting substituent (**1.12b**) the aqueous acceleration was significantly enhanced. Wijnen has also studied the reaction between cyclohexadiene and nitrosobenzene (entry 6)¹⁶⁰. This reaction has been classified by Desimoni as a type C Diels-Alder reaction^{59a}, indicating that it is insensitive to specific interactions with the solvent such as hydrogen bonding. Consequently, the aqueous rate enhancement is modest, underlining the importance of hydrogen bonding interactions

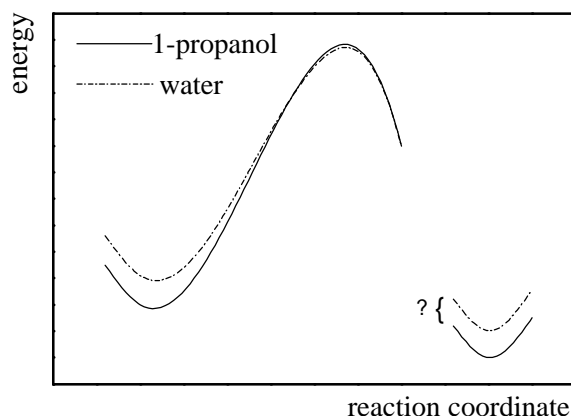


Figure 1.5. Chemical potential of the initial state, the transition state and the product of the Diels-Alder reaction between methyl vinyl ketone and cyclopentadiene in water as compared to 1-propanol. The data are taken from ref. 56.

for Diels-Alder reactions that experience large beneficial effects from water.

Further insights into the peculiar features of the Diels-Alder reaction in water can be obtained from the work of Blokzijl, who determined the Gibbs energies of transfer from 1-propanol to water of the starting materials and product of the Diels-Alder reaction between methyl vinyl ketone and ethyl vinyl ketone with cyclopentadiene⁵⁶. When combined with the Gibbs energies of activation, these data allow a direct comparison of the chemical potentials of the initial states, the transition states and the product of this reaction in these two solvents, as shown in Figure 1.5. In water the initial state is significantly destabilised relative to 1-propanol. Hydrophobic hydration of the initial state is clearly unfavourable compared to solvation in 1-propanol. Note that this also applies to the product state. The transition state, however, has nearly equal chemical potentials in water and 1-propanol. Apparently, in aqueous solution the hydrocarbon parts of the activated complex have completely lost their nonpolar character. Recent work by Meijer has confirmed this¹⁶¹. Addition of methylene units or methyl groups to the diene resulted in a destabilisation of the initial state of the Diels-Alder reaction with N-alkylmaleimides in water as compared to 1-propanol. Nevertheless, the transition states in water and 1-propanol have comparable chemical potentials. Note that, if these observations can be extrapolated to other Diels-Alder reactions, the rate of the retro Diels-Alder reaction of entry 4 will benefit from a modest hydrophobic effect.

In computer simulations Jorgensen et al.¹⁶² arrived at approximately the same conclusions. They determined the reaction path for the Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene in the gas phase, then added 500 water molecules and calculated the Gibbs energy of solvation at different stages along the reaction coordinate. Relative to the Gibbs energy of solvation of the initial state, they obtained a stabilisation of the transition state by water of 18 kJ/mole. The difference in Gibbs energy of solvation of the initial state and the product amounted to

4.6 kJ/mole in favour of the product. This estimate is in good agreement with the difference in Gibbs energy of transfer from the gas phase to water between initial and product state as tabulated for the Diels-Alder reaction of ethene with butadiene ($\Delta\Delta G_t = 6.3$ kJ/mole) and with isoprene ($\Delta\Delta G_t = 5.4$ kJ/mole)^{162a,163}. Jorgensen et al. attributed the more favourable Gibbs energy of solvation of the transition state relative to the product to an enhanced polarisation of the activated complex, accompanied by stronger hydrogen bonds. Analogous studies on the dimerisation of cyclopentadiene in water revealed a stabilisation of the transition state relative to the initial state as a result of solvation by 7.1 kJ/mole¹⁶⁴. Unfortunately, reliable experimental data on this process are not available. Recently, Furlani and Gao, following a similar approach, estimated the Gibbs energy of hydration of the Diels-Alder reaction of cyclopentadiene with isoprene and, again, methyl vinyl ketone in water¹⁶⁵. Surprisingly, the authors observed that, relative to the initial state, water stabilised the transition state of the former process more than the latter (19 kJ/mole versus 15 kJ/mole). This trend opposes the experimental data collected in Scheme 1.3, which seem to indicate that the aqueous acceleration diminishes when the hydrogen bonding interactions become impossible. Finally, the activation parameters for Diels-Alder reactions in water and a number of organic solvents have been obtained. For the reaction of methyl vinyl ketone with cyclopentadiene the acceleration on going from 1,4-dioxane to water is mainly enthalpic in origin^{87e}. Comparing water with 1-propanol the enthalpy and entropy of activation contribute about equally^{155a}. When the rate of the reaction in water is compared to that in methanol, the entropy term dominates the rate enhancement^{87f}. Analogous to the effects of Lewis-acid catalysis as described in Section 1.2.4, one may conclude that hydrogen bonding interactions mainly affect the enthalpy of activation. In contrast, the hydrophobic part of the acceleration in water is most likely mainly an entropy effect, in good agreement with the theories outlined in Section 1.3. Note that the Diels-Alder reaction in water benefits from both a reduced enthalpy of activation as well as a reduced entropy of activation. This pattern is rather unusual and can be interpreted as another indication for the simultaneous operation of two mechanisms of activation.

In summary, a wealth of experimental data as well as a number of sophisticated computer simulations univocally indicate that two important effects underlie the acceleration of Diels-Alder reactions in aqueous media: hydrogen bonding and enforced hydrophobic interactions¹⁶⁶. In terms of transition state theory: hydrophobic hydration raises the initial state more than the transition state and hydrogen bonding interactions stabilise the transition state more than the initial state. The highly polarisable activated complex plays a key role in both of these effects.

1.4.2 The effect of water on the selectivity of Diels-Alder reactions

Three years after the Breslow report on the large effects of water on the rate of the Diels-Alder reaction^{87a}, he also demonstrated that the endo-exo selectivity of this reaction benefits markedly from employing aqueous media¹⁶⁷. Based on the influence of salting-in and salting-out agents, Breslow pinpoints hydrophobic effects as the most important contributor to the enhanced endo-exo

selectivity¹⁵². Hydrophobic effects are assumed to stabilise the more compact endo transition state more than the extended exo transition state. This difference in compactness of both states is evident from the well-known smaller activation volume of the endo cycloaddition^{26b}. In Breslow's opinion, also the polarity of water significantly enhances the endo-exo selectivity¹⁵².

Likewise, Grieco, while working with amphiphile-like reactants, observed an enhanced preference for endo-adduct in aqueous solutions, which he attributed to "orientational effects" within the micelles that were presumed to be present in the reaction mixture¹⁴⁹. Although under the conditions used by Grieco, the presence of aggregates cannot be excluded, other studies have clearly demonstrated that micelle formation is not the reason for the improved selectivities^{83,247}. Micellar aggregates even tend to diminish the preference for endo adduct¹⁶⁷.

Studies on solvent effects on the endo-exo selectivity of Diels-Alder reactions have revealed the importance of hydrogen bonding interactions besides the already mentioned solvophobic interactions and polarity effects. Further evidence of the significance of the former interactions comes from computer simulations⁵⁰ and the analogy with Lewis-acid catalysis which is known to enhance dramatically the endo-exo selectivity (Section 1.2.4).

In conclusion, the special influence of water on the endo-exo selectivity seems to be a result of the fact that this solvent combines in it three characteristics that all favour formation of the endo adduct: (1) water is a strong hydrogen bond donor, (2) water is polar and (3) water induces hydrophobic interactions.

Water is also reported to increase the diastereofacial-^{62,65,168} and regioselectivity^{168,169} of Diels-Alder reactions. Mechanistic investigations have been carried out on the reaction between cyclopentadiene and (1R,2S,5R)-menthyl acrylate, which has been shown to be dominated by the hydrogen bond donor characteristics of the solvent together with its polarity^{62,65,170}.

1.4.3 The effect of additives on the rate and selectivity of Diels-Alder reactions in water.

Breslow et al. reported the effects of chaotropic and anti-chaotropic salts on the rate of aqueous Diels-Alder reactions in their first paper^{87a}. The former are salting-out agents, lowering the solubility of nonpolar compounds in water mainly by thwarting the formation of a cavity to accompany the solute. The latter act as salting-in agents, and according to Breslow, are involved in direct solvation of the solute¹⁷¹. The ensuing increased solubility can but result in decreased hydrophobic interactions and visa versa¹⁴⁸. A more systematic investigation of the salt effects on Diels-Alder reactions showed that they correlate linearly with the size of the anion¹⁷². Interestingly, Keay has reported a retardation of an intramolecular Diels-Alder reaction upon addition of lithium chloride (a salting-out agent)¹⁷³. Calcium chloride, however, increases the efficiency of this reaction²⁵³. A thermodynamic analysis of the effect of lithium chloride on the reaction between cis-dicyanoethene and cyclopentadiene reveals that the modest decrease in Gibbs energy of activation results from a dramatic decrease of the activation enthalpy that is almost completely compensated for by an

increase in the activation entropy^{87e}. This trend can be interpreted as a result of the decreased ability of aqueous lithium chloride solutions to form a hydrophobic hydration shell around diene and dienophile. Hydrophobic interactions then tend to increase and become enthalpy driven.

The effect of addition of different alcohols has been studied extensively by Blokzijl^{56,155}. The rate of the reaction between cyclopentadiene and methyl vinyl ketone decreases upon addition of alcohols. Surprisingly, a number of other Diels-Alder reactions show an increase in rate upon addition of small amounts (a few mole percent) of alcohols^{56,166c}. This trend has been explained by assuming an enhancement of hydrophobic interactions in these media. The alcohol molecules were expected to promote the water structure, which in turn would favour the entropy contribution of hydrophobic interactions^{155a}. If this were true, addition of alcohol would result in an even larger reduction of the entropy of activation of the Diels-Alder reaction. The opposite is observed^{155a}. Alternatively, enhancement of hydrophobic interactions might well be a result of a disturbing influence exerted by the alcohol molecules on the hydrophobic hydration shell. Where the activation entropy of the reaction in pure water is less unfavourable than in organic solvents due to release of hydration-shell water in the activation process, the addition of alcohol breaks down these shells and thereby brings the entropy of activation back to normal. Hence the addition of small amounts of alcohol increases the activation entropy of the Diels-Alder reaction relative to pure water. The increased hydrophobic effects will now gradually become more enthalpy-driven so the activation enthalpy is reduced upon addition of alcohol. At higher cosolvent concentrations direct alcohol - reagent contacts are suggested to occur and the rate constant decreases sharply until the value in pure alcohol is reached⁵⁶.

Breslow studied the dimerisation of cyclopentadiene and the reaction between substituted maleimides and 9-(hydroxymethyl)anthracene in alcohol-water mixtures. He successfully correlated the rate constant with the solubility of the starting materials for each Diels-Alder reaction. From these relations he estimated the change in solvent accessible surface between initial state and activated complex¹⁷⁴. Again, Breslow completely neglects hydrogen bonding interactions, but since he only studied alcohol-water mixtures, the enforced hydrophobic interactions will dominate the behaviour.

Recently, also Diels-Alder reactions in dilute salt solutions in aqueous ethanol have been studied and minor rate increases have been observed^{151b,175}. Lubineau has demonstrated that addition of sugars can induce an extra acceleration of the aqueous Diels-Alder reaction^{87f}. Also the effect of surfactants on Diels-Alder reactions has been studied. This topic will be extensively reviewed in Chapter 4.

The effect of additives on the selectivity of the Diels-Alder reaction in water has not received much attention. The scattered reports on this topic all point towards an increase in endo-exo selectivity by additives that increase hydrophobic interactions^{152,167,169}. In contrast, alcohols tend to decrease endo-exo selectivity⁵⁶.

1.4.4 Synthetic applications

A few years after the first articles of Breslow had appeared, Grieco elegantly demonstrated that the astonishing rate and selectivity enhancements of Diels-Alder reactions in water can be exploited successfully in organic synthesis. He extensively studied the reactivity of dienes containing hydrophilic carboxylate^{149,150a,b,c,176} or ammonium^{150d} groups, as well as hetero Diels-Alder reactions of iminium ions¹⁷⁷. These processes can be successfully employed in natural product synthesis^{176,178}. The extensive work of Lubineau further demonstrated the merits of water with respect to the rates and selectivities of the Diels-Alder reaction. Since 1985 he has published a large number of articles dealing mainly with dienes that were rendered water soluble through the temporary introduction of a sugar moiety^{8,87f,153a,168,179}. The efficiency of Diels-Alder reactions between these compounds and standard dienophiles is still significantly enhanced in aqueous solutions, despite the presence of the hydrophilic sugar group in the diene^{153a}. The sugar moiety could be removed after completion of the Diels-Alder reaction. Lubineau also studied the hetero Diels-Alder reactions of glyoxylic acid and its sodium salt in some detail^{8,179 d,180}. Also these reactions were shown to benefit considerably from the use of water as a solvent. Waldmann et al. studied the influence of α -amino-acid derivatives as chiral auxiliaries on the diastereoselectivity of several Diels-Alder reactions in aqueous media¹⁸¹. In contrast to the advantageous influence of the medium on rate and endo-exo selectivity, Waldmann did not observe an increase in diastereofacial selectivity^{181c}. Kibayashi et al.¹⁸² and others¹⁸³ successfully employed aqueous Diels-Alder reactions in natural product synthesis. Interestingly, also photochemical [4+2] cycloadditions benefit from aqueous media. The rate of the addition of singlet oxygen to an aromatic compound, for example, is significantly enhanced by water¹⁸⁴. Recently the scaling up of water-based Diels-Alder reactions has been studied¹⁸⁵.

1.4.5 Related water-accelerated transformations

Apart from the thoroughly studied aqueous Diels-Alder reaction, a limited number of other transformations have been reported to benefit considerably from the use of water. These include the aldol condensation³, the benzoin condensation⁷, the Baylis-Hillman reaction (tertiary-amine catalysed coupling of aldehydes with acrylic acid derivatives)¹⁸⁶ and pericyclic reactions like the 1,3-dipolar cycloaddition¹⁸⁷ and the Claisen rearrangement (see below). These reactions have one thing in common: a negative volume of activation. This observation has tempted many authors to propose hydrophobic effects as primary cause of the observed rate enhancements.

Mechanistic investigations have focused on the two pericyclic reactions, probably as a consequence of the close mechanistic relation to the so successful aqueous Diels-Alder reaction. A kinetic inquest into the effect of water on several 1,3-dipolar cycloadditions has been performed by Steiner¹⁸⁸, van Rietschoten, van Mersbergen¹⁸⁹ and Wijnen^{188,166c}. These authors demonstrated that the same two factors that underlie the acceleration of Diels-Alder reactions in water (hydrogen bonding and enforced hydrophobic interactions) also determine the rate of these [3+2] cycloadditions^{189, 166c}. Experimental studies on the effect of water on the Claisen rearrangement have been performed by Grieco¹⁹⁰, Lubineau¹⁹¹ and Gajewski¹⁹². Desimoni has observed linear correlations of the rate of the

retro-Claisen rearrangement with the $E_T(30)$ polarity parameter of the solvent, but unfortunately did not include water¹⁹³. Theoretical studies on the aqueous Claisen rearrangement have been performed by Cramer and Truhlar¹⁹⁴ and by the groups of Jorgensen¹⁹⁵, Gao¹⁹⁶ and Hillier¹⁹⁷. Theoretical as well as experimental studies have been reviewed by Ganem¹⁹⁸ and Gajewski¹⁹⁹. Surprisingly, despite its negative volume of activation, hydrophobic interactions turn out to be of secondary importance in explaining the aqueous acceleration. Hydrogen-bonding interactions were identified as the dominant factor.

In retrospect one may conclude that, when dealing with water-promoted organic transformations, hydrophobic interactions, as tempting an explanation as they may be, are sometimes overemphasised. These interactions are often accompanied and may well be overwhelmed by other effects. An often overlooked, but very important additional activation usually takes place through hydrogen-bonding interactions. Due to the small size of the water molecules, the number of hydrogen bonds that can be donated by this solvent generally exceeds the capabilities of protic organic solvents.

1.5 Lewis acid - Lewis base coordination in water

In a Lewis-acid catalysed Diels-Alder reaction, the first step is coordination of the catalyst to a Lewis-basic site of the reactant. In a typical catalysed Diels-Alder reaction, the carbonyl oxygen of the dienophile coordinates to the Lewis acid. The most common solvents for these processes are inert apolar liquids such as dichloromethane or benzene. Protic solvents, and water in particular, are avoided because of their strong interactions with the catalyst and the reacting system. Interestingly, for other catalysed reactions such as hydroformylations the same solvents do not give problems. This paradox is a result of the difference in hardness of the reactants and the catalyst involved.

1.5.1 Hard-Soft Acid-Base (HSAB) theory²⁰⁰

The Hard-Soft-Acid-Base (HSAB) theory was developed by *Pearson* in 1963²⁰¹. According to this theory, Lewis acids and Lewis bases are divided into two groups: on one hand hard acids and bases, which are usually small, weakly polarizable species with highly localised charges, and on the other hand soft acids and bases which are large, polarizable species with delocalised charges. A selection of Lewis acids, ordered according to their hardness in aqueous solution is presented in Table 1.3.

The theory predicts high stabilities for hard acid - hard base complexes, mainly resulting from electrostatic interactions and for soft acid - soft base complexes, where covalent bonding is also important. Hard acid - soft base and hard base - soft acid complexes usually have low stability. Unfortunately, in a quantitative sense, the predictive value of the HSAB theory is limited.

Thermodynamic analysis clearly shows a difference between hard-hard interactions and soft-soft interactions. 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

Table 1.3. Classification of the hardness in aqueous solution of some selected Lewis-acids according to the HSAB theory^a.

hard	borderline	soft
H ⁺	Fe ²⁺	Cu ⁺
Fe ³⁺	Ni ²⁺	Hg ⁺
Co ³⁺	Cu ²⁺	Cd ⁺
Al ³⁺	Zn ²⁺	
La ³⁺		

^a Data taken from Ref. 201a.

Lewis acid and the ligand. By contrast, soft-soft interactions are mainly enthalpic in origin and are characterised by a negative change in entropy²⁰².

Several alternative attempts have been made to quantify Lewis-acid Lewis-base interaction²⁰³. In view of the HSAB theory, the applicability of a scale which describes Lewis acidity with only one parameter will be unavoidably restricted to a narrow range of structurally related Lewis bases. The use of more than one parameter results in relationships with a more general validity²⁰⁴. However, a 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 remains largely speculative.

1.5.2 Coordination in water versus organic solvents²⁰⁵

The most effective Lewis-acid catalysts for the Diels-Alder reaction are hard cations. Not surprisingly, they coordinate to hard nuclei on the reacting system, typically oxygen atoms. Consequently, hard solvents are likely to affect these interactions significantly. Table 1.4 shows a selection of some solvents ranked according to their softness. Note that water is one of the hardest

Table 1.4. Softness of some selected solvents according to the μ -scale^a.

solvent	μ
water	0.00 ^b
methanol	0.02
dichloromethane	0.1 - 0.2 ^c
dimethyl sulfoxide	0.22
benzene	0.3 - 0.4 ^c
acetonitrile	0.35

^a Data taken from Ref. 206, derived from a comparison of $\Delta G_{tr,0}$ (water \rightarrow solvent) for Ag⁺ with the mean of $\Delta G_{tr,0}$ (water \rightarrow solvent) for Na⁺ and K⁺. ^b By definition. ^c Only approximate values are reported.

Table 1.5. Donor scales (D_S , DN and DN_{BULK}) of some selected solvents, as well as acceptor number (AN) and hydrogen bond donor capacities (α).

	D_S^a	DN ^b	DN_{BULK}^c	AN ^d	α^e
dichloromethane	6			20.4	0.00
benzene	9	0.1	0.8	8.2	(0.30)
acetonitrile	12	14.1	11.1	19.3	0.19
water	17	18.0	40.3	54.8	1.17
methanol	18	19	31.3	41.3	0.93
dimethylsulfoxide	27.5	29.8	27	19.3	0.00

^a Donor strengths, taken from ref. 207b, based upon the solvent effect on the symmetric stretching frequency of the soft Lewis acid $HgBr_2$. ^b Gutmann's donor number taken from ref. 207b, based upon ΔH_r for the process of coordination of an *isolated* solvent molecule to the moderately hard $SbCl_5$ molecule in dichloroethane. ^c Bulk donor number calculated as described in ref. 209 from the solvent effect on the adsorption spectrum of $VO(acac)_2$. ^d Taken from ref. 58, based on the ^{31}P NMR chemical shift of triethylphosphine oxide in the respective pure solvent. ^e Taken from ref. 61, based on the solvatochromic shift of a pyridinium-*N*-phenoxide betaine dye.

solvents known.

Solvents are able to affect Lewis-acid Lewis-base equilibria through a number of non-covalent interactions. First, the solvent can act as a Lewis base itself, by coordinating to the catalyst. Analogous to the Lewis acidity scales, solvents have been ranked according to their Lewis-basicity. These scales, as far as they try to quantify Lewis-basicity by using only one parameter, have limited validity. The electron-pair donor ability and Lewis-basicity scales of solvents are discussed in ref. 61 and 207. In Table 1.5 a number of Lewis acidity parameters of some relevant solvents are compared. Aprotic and apolar solvents coordinate relatively weakly to the catalyst, whereas polar solvents exhibit stronger interactions. Note that water, as bulk liquid, is among the most strongly Lewis-basic solvents when hard-hard interactions are considered. These interactions have to be disrupted before the Diels-Alder reactant can coordinate to the Lewis acid. Furthermore, steric interactions between the coordinated Diels-Alder reactant and coordinated solvent molecules are important in determining the stability of the complex²⁰⁸. Consequently, catalysis by Lewis acids in solvents that coordinate strongly to the catalyst will be less effective.

The second important influence of the solvent on Lewis acid - Lewis base equilibria concerns the interactions with the Lewis base. Consequently the Lewis acidity and, for hard Lewis bases, especially the hydrogen bond donor capacity of the solvent are important parameters. The electron pair acceptor capacities, quantified by the acceptor number AN, together with the hydrogen bond donor acidities, α , of some selected solvents are listed in Table 1.5. Water is among the solvents with the highest AN and, accordingly, interacts strongly with Lewis bases. This seriously hampers the efficiency of Lewis-acid catalysis in water.

Thirdly, the intramolecular association of a solvent affects the Lewis acid - base equilibrium²¹⁰. 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 entropically favourable. This effect is more pronounced in aprotic solvents than in protic solvents, which usually have a higher cohesive energy density. The less favourable entropy change in protic solvents is somewhat counteracted by the more favourable enthalpy change upon release of a coordinated solvent molecule into the bulk liquid, resulting from the newly formed hydrogen bonds.

Finally, the solvent also interacts with sites of the Lewis acid and the Lewis base that are not directly involved in mutual coordination, thereby altering the electronic properties of the complex. For example, delocalisation of charges into the surrounding solvent molecules causes ions in solution to be softer than in the gas phase²⁰⁸. Again, water is particularly effective since it can act as an efficient electron pair acceptor as well as a donor.

In summary, water is clearly an extremely bad solvent for coordination of a hard Lewis acid to a hard Lewis base. 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 in this medium.

1.6 Motivation, aims and outline of this study

In the previous sections a large number of studies have been reviewed demonstrating that rates and selectivities of Diels-Alder reactions increase dramatically when aqueous reaction media are used. Hydrogen-bonding interactions and enforced hydrophobic interactions are likely to underlie these effects. Synthetic applications are extensive, but unfortunately mainly limited to compounds that are rendered water soluble through the introduction of ionic or polar groups. Alternatively, decades before the remarkable effect of water on Diels-Alder reactions was discovered, it was already known that Lewis acids were extremely effective in increasing the rate and the selectivity of these transformations in many organic solvents.

A combination of the promoting effects of Lewis acids and water is a logical next step. However, to say the least, water has not been a very popular medium for Lewis-acid catalysed Diels-Alder reactions, which is not surprising since water molecules interact strongly with Lewis-acidic and the Lewis-basic atoms of the reacting system. In 1994, when the research described in this thesis was initiated, only one example of Lewis-acid catalysis of a Diels-Alder reaction in water was published: Lubineau and co-workers employed lanthanide triflates as a catalyst for the Diels-Alder reaction of glyoxylate to a relatively unreactive diene^{180b}. No comparison was made between the process in water and in organic solvents.

In view of the remarkable effects that water can exert on the uncatalysed Diels-Alder reaction, there might well be a similar effect on the rate and the selectivity of the Lewis-acid catalysed process. At the same time, coordination of a Lewis-acid to a Diels-Alder reagent is likely to overcome the

solubility problems frequently encountered with these compounds. Finally, the ultimate challenge would be to study the effect of water on the enantioselectivity of a chiral Lewis-acid catalysed reaction. For as far as we know, no example of a homogeneous chiral Lewis-acid catalysed Diels-Alder reaction has been reported before. Actually, we are not aware of the existence of any other homogeneous organic transformation that is successfully catalysed by chiral Lewis-acids in water.

In summary, the following questions will be addressed in this thesis:

1. What is the effect of water on the rate and selectivity of the Lewis-acid catalysed Diels-Alder reaction, when compared to organic solvents ? Do hydrogen bonding and hydrophobic interactions also influence the Lewis-acid catalysed process ? Answers to these questions will be provided in Chapter 2.
2. What is the influence of ligands on the Lewis acid on the rate and selectivity of the Diels-Alder reaction ? If enantioselectivity can be induced in water, how does it compare to other solvents ? Chapter 3 deals with these topics.
3. What is the scope of Lewis-acid catalysis of Diels-Alder reactions in water ? An approach of extending the scope by making use of a temporary secondary coordination site is described in Chapter 4.
4. What is the effect of micelles on the aqueous Diels-Alder reaction ? Can micellar catalysis be combined with Lewis-acid catalysis ? In Chapter 5 these aspects will be discussed.

Finally, Chapter 6 will provide an overview and some important conclusions will be drawn concerning the use of aqueous media in organic chemistry with a special emphasis on catalysis.

Most of the work described in this thesis has been published^{157,161,211}.

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Notes and references

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Lewis-Acid Catalysis¹

Many Diels-Alder reactions can be catalysed efficiently by Lewis acids in organic solvents. It is also known that the use of water as a solvent has a favourable effect on rate and selectivity of these reactions. A detailed investigation of the possibilities of combining both effects has hitherto not been reported and forms the goal of this chapter. It will be demonstrated that Lewis-acid catalysis of a Diels-Alder reaction in aqueous media is feasible and can actually lead to astonishing increases in the rate of the reaction. A detailed study of the kinetics of this process will be presented, alongside with results of investigations of the complexation behaviour of the Diels-Alder reagents to a number of different Lewis acids in aqueous solution. Also the effects of Lewis acids on the endo-exo selectivity in water will be described and compared to the corresponding effects in organic solvents.

2.1 Introduction

The Diels-Alder reaction is often quoted as an example of a reaction that is little influenced by the solvent. However, this is not fully justified, since particularly water can have a pronounced effect on the rate of this reaction. This was first noticed by Eggelte et al.² in 1973 and rediscovered in 1980 by Breslow³. In the years that followed this intriguing discovery, it turned out that acceleration of Diels-Alder reactions by water is a general phenomenon that can ultimately result in up to 12,800 fold accelerations⁴. Synthetic applications followed rapidly⁵.

Mechanistic studies have tried to unravel the origin of the special effect of water. Some authors erroneously have held aggregation phenomena responsible for the observed acceleration⁶, whereas others have hinted at effects due to the internal pressure⁷. However, detailed studies have identified two other effects that govern the rate of Diels-Alder reactions in water.

In the first place *enforced hydrophobic interactions* are important⁸. The initial state of the Diels-Alder reaction is significantly destabilised in water relative to organic solvents, due to the relatively unfavourable solvation of the apolar moieties in aqueous solution. During the activation process the apolar character of the groups near the reaction centre is largely lost⁹. Consequently, the transition state is hardly destabilised by water and, hence, the reaction is accelerated. The term “enforced” has been introduced to stress the fact that it is the occurrence of the organic reaction that gives rise to the hydrophobic interaction, whereas the hydrophobic interaction is, in itself, not strong enough to bring the reactants together.

Hydrogen bonding of water to the activating group of (for normal-electron demand Diels-Alder reactions) the dienophile constitutes the second important effect^{4,10}. Hydrogen bonds strengthen the electron-withdrawing capacity of this functionality and thereby decrease the HOMO-LUMO gap

between diene and dienophile.

The relative extents to which enforced hydrophobic interactions and hydrogen bonding influence the rate of the Diels-Alder reaction depends on the particular reaction under study¹¹.

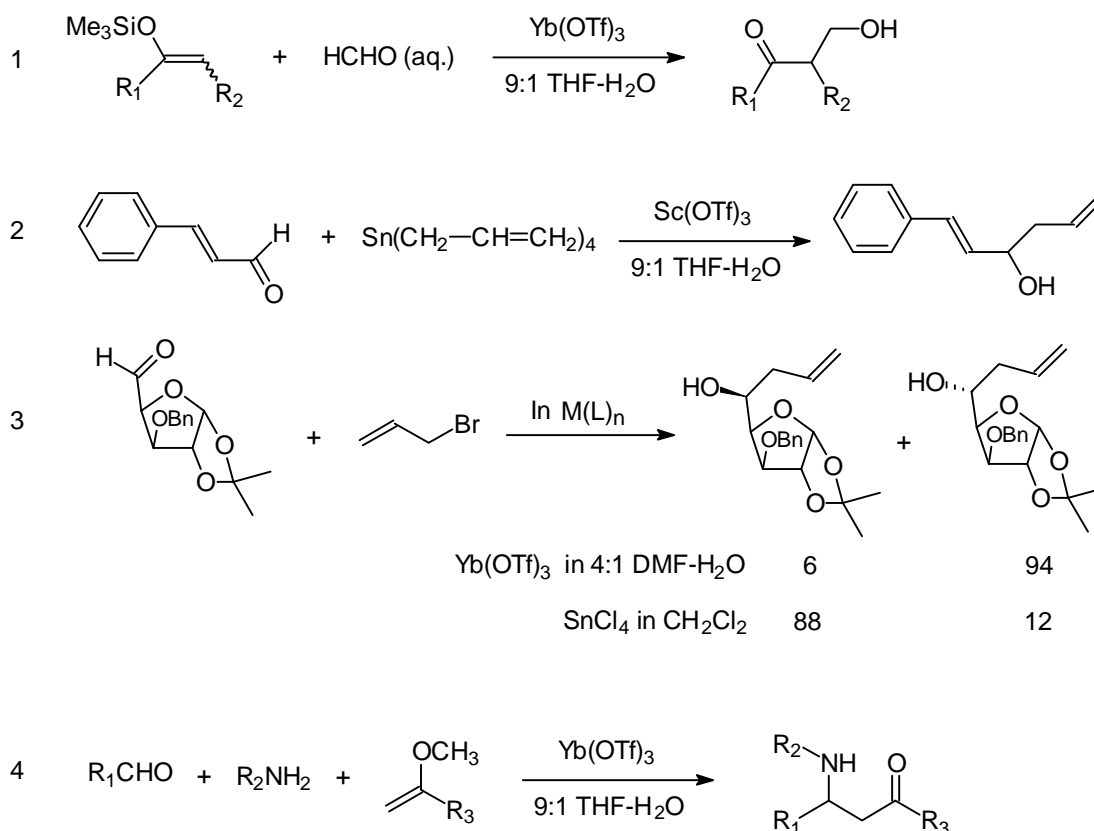
The appreciable rate effects in water are generally overshadowed by the large accelerations that can be induced in organic solvents by coordinating a Lewis-acid catalyst to the activating group of (for normal electron demand Diels-Alder reactions) the dienophile¹². Analogous to the hydrogen bonding effect, Lewis acids can decrease the HOMO-LUMO gap between diene and dienophile and thereby induce an increase of the rate of the reaction.

Appreciating the beneficial influences of water and Lewis acids on the Diels-Alder reaction and understanding their origin, one may ask what would be the result of a combination of these two effects. If they would be additive, huge accelerations can be envisaged. But may one really expect this? How does water influence the Lewis-acid catalysed reaction, and what is the influence of the Lewis acid on the enforced hydrophobic interaction and the hydrogen bonding effect? These are the questions that are addressed in this chapter.

In order to be able to provide answers to these questions, a Diels-Alder reaction is required that is subject to Lewis-acid catalysis in aqueous media. Finding such a reaction was not an easy task. Fortunately the literature on other Lewis-acid catalysed organic reactions in water was helpful to some extent.

*2.1.1 Lewis-acid catalysis of organic reactions in aqueous solutions*¹³

The demand for environmentally friendly chemistry has made the use of water as a solvent for organic transformations increasingly popular^{5,14}. However, this trend does not seem to extend to Lewis-acid catalysis, at least not when pure water is considered. Mixtures of organic solvents and water (typically 9:1 mixtures of THF and water), on the other hand, are now commonly employed media for a number of organic transformations¹⁵. One example is the Lewis-acid catalysed *aldol reaction*, commonly known as the Mukaiyama aldol reaction, of silyl enol ethers, which was first reported in the early seventies¹⁶. With titanium tetrachloride as catalyst this reaction proceeds in a regioselective manner, giving high yields. These transformations were traditionally carried out under strictly non-aqueous conditions to prevent decomposition of the catalyst and hydrolysis of the silyl enol ethers used in the reaction. The same reaction in the absence of catalyst was previously studied by Lubineau, who observed that water had a beneficial influence on this process¹⁷. However, the scope and yields were not satisfactory. In 1991, Kobayashi reported the first Lewis-acid catalysed cross aldol reaction in an aqueous mixture¹⁸. He examined the effects of lanthanide triflates on the reaction of several silyl enol ethers with a commercial formaldehyde solution (entry 1 in Scheme 2.1). The reactions were most effectively carried out in a 1:9 commercial aqueous formaldehyde-THF mixture under the influence of 5-10 mole percent of Yb(OTf)₃, which can be reused after completion of the reaction¹⁹. Various aldehydes could be used²⁰. The amount of water in the reaction mixture is crucial. The best results were obtained when the organic solvent contained 10-20% (v/v) of water. When the amount of water was increased, the yield of aldol product decreased. This



Scheme 2.1. Lewis-acid catalysed organic reactions that are promoted by small amounts of water in organic solvents.

fall in yield was attributed to the competitive hydrolysis of the silyl enol ether.

The use of indium in aqueous solution has been reported by Li and co-workers as a new tool in organometallic chemistry²¹. Recently Loh reported catalysis of the Mukaiyama-aldol reaction by indium trichloride in aqueous solution²². He attributed the beneficial effect of water to aggregation phenomena in connection with the high internal pressure of this solvent²³. This work has been severely criticised by Kobayashi²⁴.

Lewis-acid catalysed *allylation reactions* also benefit from the presence of water as a cosolvent. The synthesis of homoallylic alcohols via a Lewis-acid catalysed reaction of organometallic reagents with a carbonyl compound in organic media has been frequently reported²⁵. The first example of such a Lewis-acid catalysed allylation reaction in aqueous medium was again reported by Kobayashi²⁶. In a smooth reaction under the influence of 5 mole percent of Sc(OTf)₃, tetraallyltin was allowed to react with several ketones and aldehydes (an example is given in entry 2 in Scheme 2.1). The reactions were carried out in water-THF, water-ethanol or water-acetonitrile mixtures (1:9) providing high yields of the corresponding homoallylic alcohol. The much cheaper Yb(OTf)₃ is also effective in this reaction and the Lewis acid can be reused without loss of activity¹⁹. Loh has demonstrated that indium can be used to promote the allylation of aldehydes and ketones in water at room temperature without the need of an inert atmosphere²⁷. The use of a Lewis-acid promotor in this reaction can have a large effect on the stereoselectivity²⁸. Furthermore the

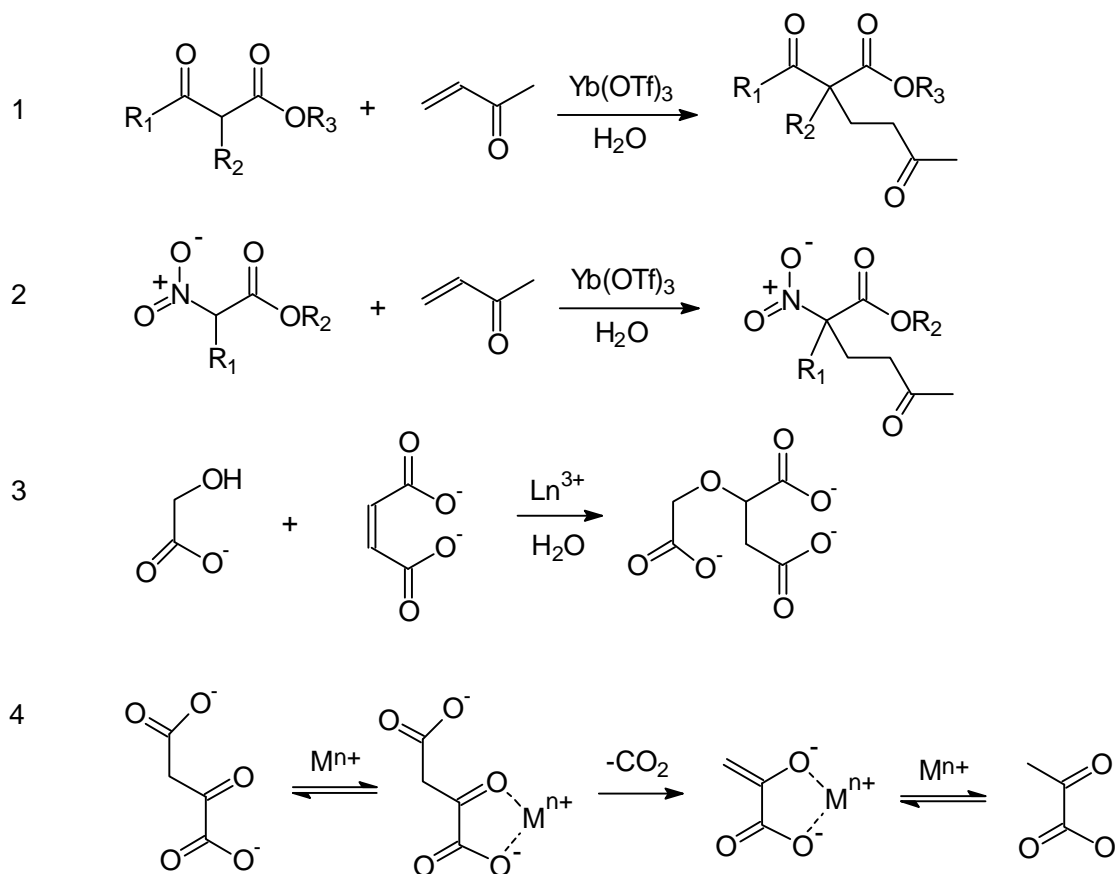
reaction time was significantly reduced. Compared to the reaction under aprotic conditions, in which case allylsilane was used instead of allylbromide/indium, almost complete reversal of diastereoselectivity was found (entry 3 in Scheme 2.1). Recently it has been demonstrated that pure water and particularly saturated ammonium chloride solutions promote the Lewis-acid catalysed allylation efficiently²⁹.

Finally, Lewis-acid catalysed *Mannich reactions* can be carried out conveniently in a mixture of organic solvent and water. An aldehyde, an amine and a vinyl ether have react in THF-water (9:1) mixtures, in the presence of 10 mole percent of Yb(OTf)₃, to give the β-amino ketone in 55-100 % yield (entry 4 in Scheme 2.1)³⁰. The exact role of the Lewis acid in this reaction has not been clarified. Recently, Loh reported an indium trichloride catalysed Mannich-type reaction in water³¹.

Relatively few examples of organic transformations are known that are catalysed efficiently by Lewis acids in water in the absence of an organic (co)solvent. One such example is the lanthanide-ion catalysed *Michael addition*. The use of water as a solvent in the uncatalysed Michael addition of 1,3-diketones had already been reported occasionally³². The corresponding reaction of β-ketoesters did not give satisfactory results³³. However, Keller et al. demonstrated that upon introduction of a catalytic amount of Yb(OTf)₃ a large range of β-ketoesters react efficiently with various β-unsubstituted enones (entry 1 in Scheme 2.2)³⁴. Likewise, α-nitroesters smoothly undergo Lewis-acid catalysed Michael additions in water (entry 2 in Scheme 2.2)³⁵. Van Bekkum and co-workers studied a lanthanide-ion catalysed Michael-like addition of glycolate to maleate (entry 3 in Scheme 2.2)³⁶. Extensive mechanistic studies demonstrated that this reaction proceeds through a ternary complex, wherein attack of coordinated and double deprotonated glycolate on the coordinated maleate dianion is rate limiting.

Perhaps the most extensively studied catalytic reaction in aqueous solutions is the metal-ion catalysed *hydrolysis* of carboxylate esters³⁷, phosphate esters³⁸, phosphate diesters³⁹, amides^{36b,37f,40} and nitriles⁴¹. Inspired by hydrolytic metalloenzymes, a multitude of different metal-ion complexes have been prepared and analysed with respect to their hydrolytic activity. Unfortunately, the exact mechanism by which these complexes operate is not completely clarified⁴². The most important role of the catalyst is coordination of a hydroxide ion that is acting as a nucleophile. The extent of activation of the substrate through coordination to the Lewis-acidic metal centre is still unclear and probably varies from one substrate to another. For monodentate substrates this interaction is not very efficient. Only a few quantitative studies have been published. Chin et al. reported an equilibrium constant for coordination of the amide carbonyl group of formylmorpholine to a cobalt(III) catalyst of $0.4 \pm 0.1 \text{ M}^{-1}$ ⁴³. The same catalyst coordinates acetonitrile in water with an equilibrium constant^{41d} of 2.5 M^{-1} .

Examples of metal-ion catalysed organic reactions in water where the catalyst acts exclusively as Lewis acid are the *bromination* of diketones⁴⁴ and the *decarboxylation* of oxaloacetate. The latter reaction has been studied in detail. In 1941 it was demonstrated that magnesium(II) ions catalyse this reaction⁴⁵. Later also catalysis by other multivalent metal ions, such as Zn(II), Mn(II), Cu(II), Cd(II), Fe(II), Pb(II), Fe(III) and Al(III) was reported⁴⁶. Likewise, trivalent lanthanide ions were found to promote the decarboxylation⁴⁷. A large number of mechanistic studies have established the mechanism of the catalysed reactions, which is



Scheme 2.2. Lewis-acid catalysed reactions in pure water.

outlined in entry 4 in Scheme 2.2⁴⁸. Similarly, acetonedicarboxylic acid has been observed to undergo Lewis-acid catalysed decarboxylation⁴⁹. Later studies have focused on the effects of ligands on the efficiency of the catalysed reaction⁵⁰. This topic will be discussed extensively in Chapter 3.

In summary, only for a limited number of Lewis-acid catalysed reactions mechanistic studies have been published. Invariably, these studies involve bidentate substrates⁵¹. In the majority of reports on Lewis-acid catalysed transformations in (heterogeneous) aqueous media little attention is paid to the mechanism underlying these reactions. A large number of these studies make use of lanthanide ions. In some cases monodentate substrates are used and coordination of the lanthanide ion to a carbonyl group is assumed. However, Richardson stated that: “In aqueous solutions, donor groups containing neutral oxygen or nitrogen atoms generally bind (or occupy Ln^{3+} coordination sites) *only* when present in multidentate ligands that contain at least one or two other donor groups having negatively charged oxygens.”⁵² Hence, instead of Lewis-acid catalysis, the beneficial effect of the presence of Lewis-acids on the efficiency of these reactions might well be indirect. For instance, Brønsted-acid or base catalysis can be expected to be operative. Solutions of Lewis-acid ions in water are modestly acidic, which indicates the simultaneous presence of lanthanide-ion coordinated hydroxide ion as well as free protons. Clearly, detailed mechanistic studies are required to identify the exact mechanism through which the presence of Lewis acids affects these reactions.

2.1.2 Lewis-acid catalysis of Diels-Alder reactions in aqueous solutions

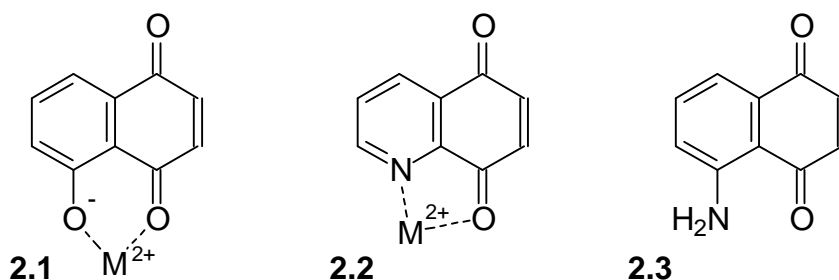
There is a growing number of examples of Lewis-acid catalysed Diels-Alder reactions that tolerate the presence of small amounts of water⁵³ or even benefit from it⁵⁴. Going one step further, Kobayashi has reported catalysis of the Diels-Alder reaction between naphthoquinone and cyclopentadiene by scandium triflate in a 90:10 THF - water mixture⁵⁵. Unfortunately, no comparison was made with the reaction in the absence of the catalyst, which is known to proceed rapidly at ambient temperature. The first example of a Lewis-acid catalysed Diels-Alder reaction in pure water can be found in a paragraph in an article on aqueous hetero Diels-Alder chemistry by Lubineau⁵⁶. He observed a quantitative reaction of glyoxylate with 2-methyl-1-3-pentadiene in the presence of lanthanide triflates after 12 hours at 60 °C. In the absence of catalyst the reaction gave 55% yield under the same conditions. Very recently, Wang and co-workers observed catalysis of an aza-Diels-Alder reaction by lanthanide(III)triflates in water⁵⁷. In this process in situ formation of the hetero dienophile is followed by the actual Diels-Alder reaction. The role of the catalyst is still unclear. Interestingly Grieco et al. have studied the reversal of this process, and observed catalysis by copper(II)sulfate⁵⁸. Loh et al. claim catalysis of an extensive number of Diels-Alder reactions by indium trichloride in water⁵⁹. However, this work has been criticised by Kobayashi⁶⁰. Likewise, kinetic experiments by the author of this thesis have failed to demonstrate any catalytic effect of indium trichloride on the prototypical Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene under homogeneous conditions. Zhu and Espenson have studied the effect of methylrhenium trioxide on a number of Diels-Alder reactions under heterogeneous conditions in aqueous solution⁶¹. These authors also report a kinetic study on the effect of their catalyst on the Diels-Alder reaction of methyl vinyl ketone with cyclopentadiene under homogeneous conditions. Unfortunately, these kinetic experiments could not be reproduced in our hands.

2.2 Results and discussion

Searching for a suitable system for studying Lewis-acid catalysis of Diels-Alder reactions in water, several points have to be considered.

First, the use of water limits the choice of Lewis-acid catalysts. The most active Lewis acids such as BF_3 , TiCl_4 and AlCl_3 react violently with water and cannot be used. However, bivalent transition metal ions and trivalent lanthanide ions have proven to be active catalysts in aqueous solution for other organic reactions and are anticipated to be good candidates for the catalysis of aqueous Diels-Alder reactions.

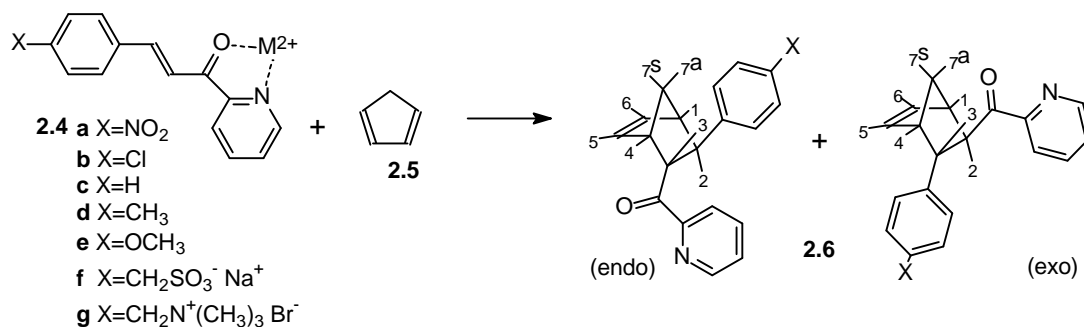
Furthermore, the number of diene - dienophile combinations that can be expected to undergo a Lewis-acid catalysed Diels-Alder reaction is limited. Studies by Wijnen leave little doubt that the rate of typical Diels-Alder reactions, where the dienophile is activated by one or more carbonyl functionalities, does not respond to the presence of Lewis acids in aqueous solution^{11d}, at least not beyond the extent that is expected for non-specific interactions (salt effects). No coordination of the Lewis acid to the dienophile was observed in these cases, which is perhaps not surprising. Water is



Scheme 2.3. Unsuccessful attempts⁶³ to catalyze Diels-Alder reactions in water. $M = \text{Zn}^{2+}$ or Cu^{2+} .

about the worst solvent one can imagine with respect to hard Lewis acid - Lewis base interactions, since water itself interacts extremely efficiently with the Lewis acid as well as the Lewis base (see section 1.5.2). Interestingly, as far as we know, all the examples of organic reactions where proof exists that true Lewis-acid catalysis takes place involve *bidentate* substrates⁶². Apparently interaction of monodentate compounds with Lewis acids in water is not strong enough to allow efficient catalysis. But even when bidentate coordination is achieved, success is not guaranteed, as is demonstrated by the examples in Scheme 2.3⁶³. Juglone (**2.1**) binds efficiently to bivalent zinc and copper ions but is deactivated upon coordination due to the deprotonation of the hydroxyl moiety. Alternatively, **2.2** is activated, but more towards undesired reactions (among them the Michael addition of water) than towards the Diels-Alder addition. Catalysis of the reaction of **2.3** was not successful either, since this compound showed little to no tendency to coordinate to hard metal ions in aqueous solution.

Fortunately, azachalcone derivatives (**2.4a-g**, Scheme 2.4) turned out to be extremely suitable dienophiles for Lewis-acid catalysed Diels-Alder reactions with cyclopentadiene (**2.5**). This reaction is outlined in Scheme 2.4 and a large part of this thesis will be devoted to the mechanistic details of this process. The presence of a chromophore in **2.4** allows kinetic studies as well as complexation studies by means of UV-vis spectroscopy. Furthermore, the reactivity of **2.4** is such that also the



Scheme 2.4.

uncatalysed reaction can be followed, allowing quantitative comparison with the catalysed reaction.

2.2.1 Synthesis

The synthesis of 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**2.4c**) via an aldol reaction of 2-acetylpyridine with benzaldehyde has been described in the literature⁶⁴. Compound **2.4a-e** have been prepared in high yields, using slightly modified versions of these literature procedures.

The highly water-soluble dienophiles **2.4f** and **2.4g** have been synthesised as outlined in Scheme 2.5. Both compounds were prepared from p-(bromomethyl)benzaldehyde (**2.8**) which was synthesised by reducing p-(bromomethyl)benzotrile (**2.7**) with diisobutylaluminium hydride following a literature procedure⁶⁵. **2.4f** was obtained in two steps by conversion of **2.8** to the corresponding sodium sulfonate (**2.9**), followed by an aldol reaction with 2-acetylpyridine. In the preparation of **2.4g** the sequence of steps had to be reversed. Here, the aldol condensation of **2.8** with 2-acetylpyridine was followed by nucleophilic substitution of the bromide of **2.10** by trimethylamine. Attempts to prepare **2.4f** from **2.10** by treatment with sodium sulfite failed, due to decomposition of **2.10** under the conditions required for the substitution by sulfite anion.

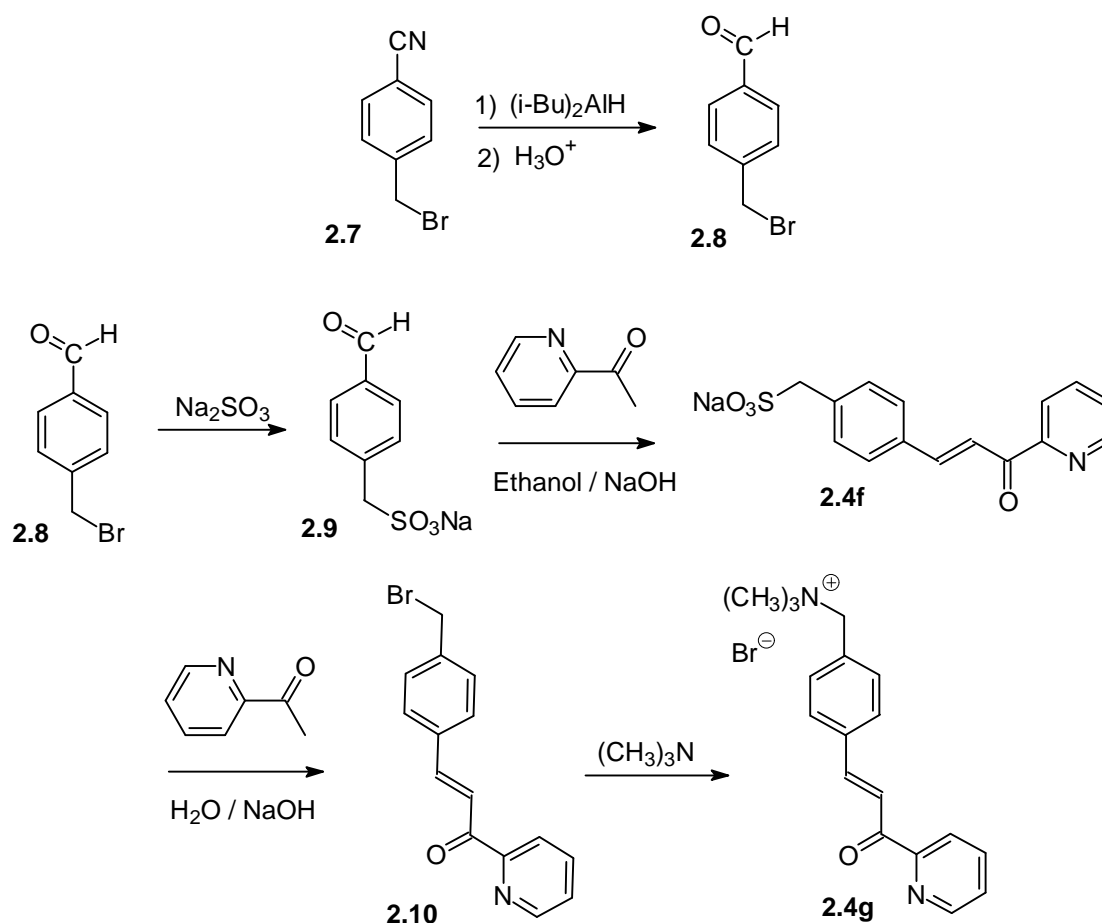
Table 2.1. Second-order rate constants (k_2) for the uncatalysed Diels-Alder reaction of **2.4a** and **2.4g** with **2.5** in different solvents at 25°C.

solvent	2.4a		2.4g
	k_2 (M ⁻¹ s ⁻¹)	k_{rel} ^a	k_2 (M ⁻¹ s ⁻¹)
acetonitrile	$1.40 \cdot 10^{-5}$	1	
ethanol	$3.83 \cdot 10^{-5}$	2.7	$2.22 \cdot 10^{-5}$
water	$4.02 \cdot 10^{-3}$	287	$2.45 \cdot 10^{-3}$
2,2,2-trifluoroethanol	$6.75 \cdot 10^{-3}$	482	

^a Rate constant relative to the reaction in acetonitrile.

2.2.2 Effect of the solvent on the rate of the uncatalysed reaction.

Before elaborating on the effect of Lewis acids on the Diels-Alder reaction of **2.4** with **2.5**, some

**Scheme 2.5.** Synthesis of the ionic dienophiles **2.4f** and **2.4g**.

features of the uncatalysed reaction will be discussed. The kinetics of the Diels-Alder reaction of **2.4**

with **2.5** can be studied by following the disappearance of the absorbance of the dienophile using UV-vis spectroscopy⁶⁶. In the absence of catalysts, the rate of the reaction is low, so that initial rate methods are required in order to obtain reliable rate constants. Of the dienophiles, **2.4a** is the most reactive, as is expected for a normal electron demand Diels-Alder reaction on the basis of FMO considerations (see Section 1.2.2). **2.4b-e** are increasingly less reactive and unfortunately, the Diels-Alder reaction of these compounds cannot compete with spontaneous decomposition. Both ionic dienophiles turned out to be sufficiently stable. The second-order rate constants of the reaction of **4.2a** and **4.2g** have been determined in water and three organic solvents. The results are shown in Table 2.1.

The solvents listed in Table 2.1 were chosen to cover a broad range in solvent properties. In fact hexane was initially also among them, but unfortunately the rate of the reaction in this solvent is extremely low. It turned out that in this solvent spontaneous decomposition of **2.4a** competes with the Diels-Alder reaction.

It is obvious that the reaction is accelerated markedly by water. However, for the first time, the Diels-Alder reaction is not fastest in water, but in 2,2,2-trifluoroethanol (TFE). This might well be a result of the high Brønsted acidity of this solvent. Indirect evidence comes from the pH-dependence of the rate of reaction in water (Figure 2.1). Protonation of the pyridyl nitrogen obviously accelerates the reaction.

Comparison of the water-induced acceleration of the reaction of **2.4a** with the corresponding effect on **2.4g** is interesting, since **2.4g** contains an ionic group remote from the reaction centre. The question arises whether this group has an influence on the acceleration of the Diels-Alder reaction by water. Comparison of the data in Table 2.1 demonstrates that this is not the case. The acceleration upon going from ethanol to water amounts a factor 105 (± 10) for **2.4a** versus 110 (± 11) for **2.4g**. Apparently, the introduction of a hydrophilic group remote from the reaction centre has no effect on the aqueous acceleration of the Diels-Alder reaction.

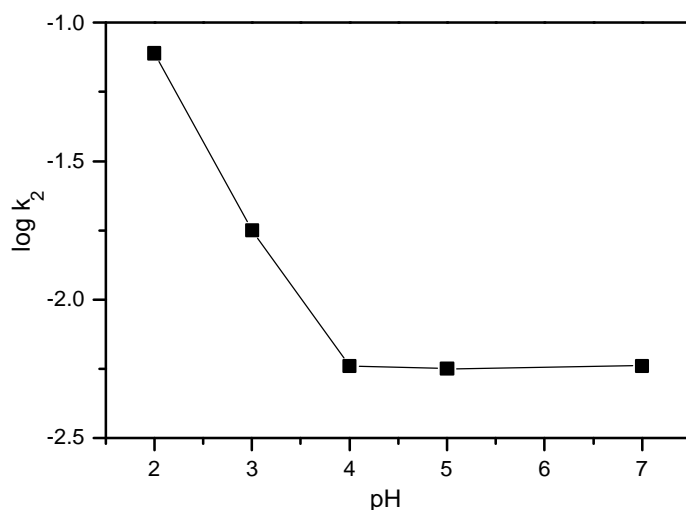


Figure 2.1. pH Dependence of the rate of the Diels-Alder reaction between **2.4a** and **2.5** in water at 25 °C.

2.2.3 Solvent and substituent effects on the Cu²⁺-catalysed reaction

The rate of the uncatalysed reaction in all four solvents is rather slow. (The half-life at [2.5] = 1.00 mM is at least 28 hours). However, upon complexation of Cu²⁺ ion to **2.4a-g** the rate of the Diels-Alder reaction between these compounds and **2.5** increases dramatically. Figure 2.2 shows the apparent rate of the Diels-Alder reaction of **2.4a** with **2.5** in water as a function of the concentration of copper(II)nitrate. At higher catalyst concentrations the rate of the reaction clearly levels off, most likely due to complete binding of the dienophile to the catalyst. Note that in the kinetic experiments

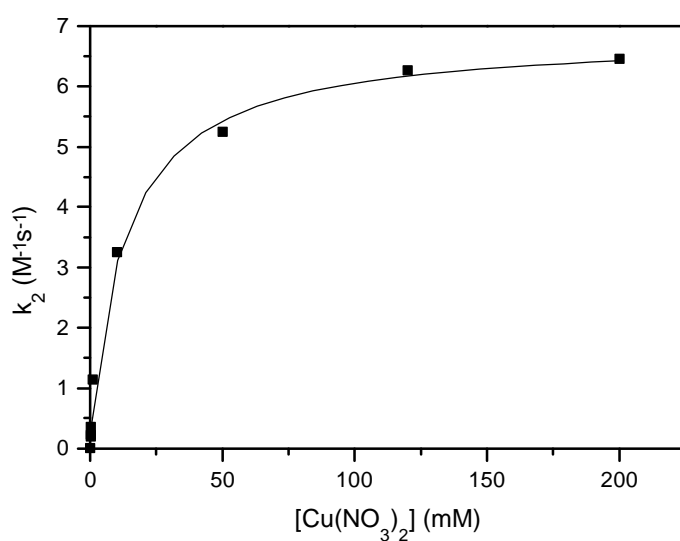


Figure 2.2. Second-order rate constant for the Diels-Alder reaction of **2.4a** with **2.5** in aqueous solution as a function of the concentrations of copper(II)nitrate.

Table 2.2. Apparent second-order rate constants (k_{app}) for the Cu^{2+} -ion catalysed reaction of **2.4a** and **2.4g** with **2.5** and ratios of the rate constants for the catalysed and uncatalysed reaction in different solvents at 25 °C.

solvent	[Cu^{2+}] (mM)	2.4a		2.4g
		k_{app} ($\text{M}^{-1}\text{s}^{-1}$)	$k_{app} / k_{uncat.}$	k_{app} ($\text{M}^{-1}\text{s}^{-1}$)
acetonitrile	10	2.21	$1.58 \cdot 10^6$	0.497
ethanol	10	0.769	$2.01 \cdot 10^4$	0.543
water	10	3.25	$8.08 \cdot 10^2$	2.13
2,2,2-trifluoroethanol	0.10	15.6	$2.31 \cdot 10^3$	

the concentration of the catalyst is orders of magnitude higher than the concentration of dienophile. Use of an excess of catalyst is inevitable when using UV-vis techniques and therefore very low concentrations of **2.4**.

In organic solvents Lewis-acid catalysis also leads to large accelerations of the Diels-Alder reaction. Table 2.2 shows the rate constants for the Cu^{2+} -catalysed Diels-Alder reaction between **2.4a** and **2.5** in different solvents.

Relative to the uncatalysed reaction in acetonitrile, the presence of Lewis acids leads to accelerations in the order of 10^6 - 10^7 . The relatively large solvent effect of water observed in the uncatalysed reaction (Table 2.1) is strongly diminished for the catalysed reaction. This trend can be rationalised as follows. For the Lewis-acid catalysed reactions the hydrogen bonding part of the acceleration will be largely taken over by the Lewis-acid, so it is likely that only the hydrophobic effect will remain. This contribution will not be unaffected by the catalyst either, since the catalyst will partly destroy the hydrophobic character of the hydration shell of the dienophile in the initial state. This will result in a significantly smaller aqueous solvent effect on the catalysed reaction. Note that the effect of the catalyst in acetonitrile, quantified by the ratio of the rate constants for the catalysed reaction and the uncatalysed counterpart, is larger than in any of the protic solvents. This trend further underlines the observation that the activation of Diels-Alder reactions by hydrogen-bonding and by Lewis-acid catalysis are not additive.

Surprisingly, the highest catalytic activity is observed in TFE. One might envisage this to be a result of the poor interaction between TFE and the copper(II) cation, so that the cation will retain most of its Lewis-acidity. In the other solvents the interaction between their electron-rich hetero atoms and the cation is likely to be stronger, thus diminishing the efficiency of the Lewis-acid catalysis. The observation that $\text{Cu}(\text{NO}_3)_2$ is only poorly soluble in TFE and much better in the other solvents used, is in line with this reasoning.

Rate constants for the Diels-Alder reaction of **2.4b-e** have also been determined. The results are shown in Table 2.3. These data allow an analysis of the influence of substituents on the Lewis-acid catalysed Diels-Alder reaction. This is interesting, since there are indications for a relatively large

Table 2.3. Apparent second-order rate constants ($M^{-1}s^{-1}$) of the Cu^{2+} -catalysed Diels-Alder reaction of **2.4b-e** with **2.5** in different solvents at 25°C.

solvent	2.4b	2.4c	2.4d	2.4e	2.4g
acetonitrile	0.594	0.472	0.240	0.0689	0.497
ethanol	0.382	0.309	0.162	0.0510	0.543
water	1.23	1.11	0.654	0.262	2.13
2,2,2-trifluoroethanol	3.31	3.22	1.52	0.549	

charge separation in the activated complex of the catalysed reaction compared to the uncatalysed one in organic solvents⁶⁷. This charge separation might induce a larger effect of substituents on the rate of the catalysed reaction. The data of Table 2.3 have been analysed in terms of the Hammett equation⁶⁸:

$$\log\left(\frac{k_x}{k_0}\right) = \rho \cdot \sigma_x \quad (2.1)$$

Herein k_x is the rate constant for a dienophile with substituent x ; k_0 is the corresponding rate constant for unsubstituted **2.4c**; σ_x is the substituent constant for substituent x and ρ is the reaction constant, defined as the slope of the plot of $\log(k_x/k_0)$ versus σ_x . The parameter ρ is a measure of the sensitivity of the reactions towards introduction of substituents. Figure 2.3 and Table 2.4 show the results of correlating the kinetic data for the reaction of **2.4a-e** with **2.5** with σ^+ .

The fact that good correlations are observed with σ^+ rather than with σ , is indicative of a strong influence of the substituent through a direct resonance interaction with a positive charge in the reacting system. The ρ -values are positive, which is expected for substituted dienophiles in a normal electron demand Diels-Alder reaction. Furthermore, the ρ -values do not exceed unity and are not significantly different from literature values reported for the uncatalysed reaction⁶⁹. It is tempting to

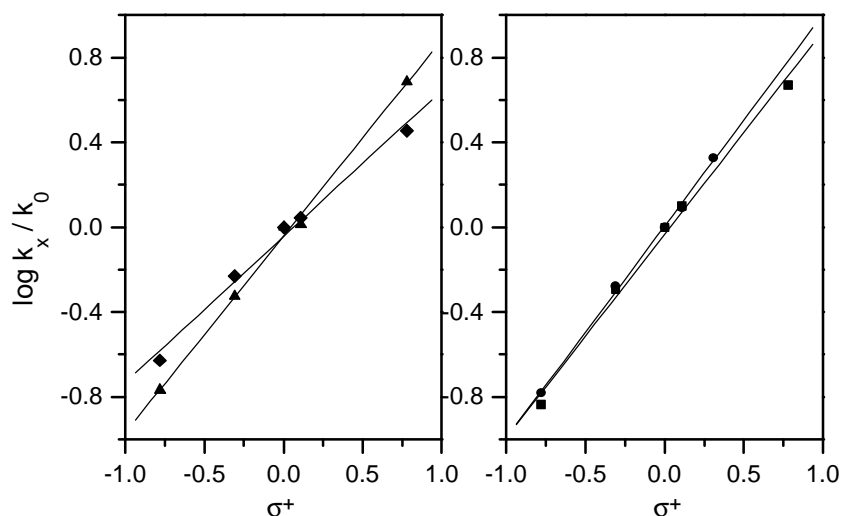


Figure 2.3. Hammett plots for the Diels-Alder reaction of **2.4a-e** with **2.5** in water (◆); 1,1,1-trifluoroethanol (▲); ethanol(●) and acetonitrile (■).

Table 2.4. Solvent effect on the Hammett ρ -values for the Diels-Alder reaction of **2.4** with **2.5** catalysed by $\text{Cu}(\text{NO}_3)_2$ at 25°C.

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

^a For unknown reasons the point for **2.4a** in the Hammett plot for ethanol strongly deviates from the otherwise good correlation. The data for **2.4a** in ethanol have therefore not been used in the calculation of ρ . Instead the data for another compound **2.4** with $\text{X} = \text{CO}_2\text{CH}_3$ ($k_2 = 0.655 \text{ M}^{-1}\text{s}^{-1}$) were used in the correlation.

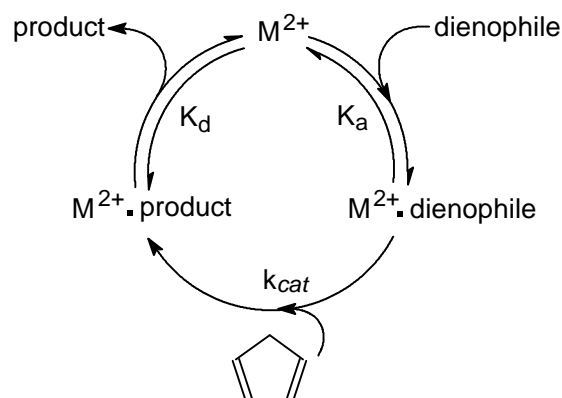
conclude that the charge separation in the activated complex of the catalysed reactions is also not significantly different from that in the uncatalysed reaction. However this conclusion is not valid. Since it is reasonable to assume that the initial state of the catalysed reaction (the dienophile - Lewis-acid complex) is more polarised than the initial state of the uncatalysed reaction, it is not justified to make a direct comparison between the activated complexes of the rate-limiting step for the uncatalysed and catalysed reactions simply on the basis of ρ -values. Moreover, the ρ -values are likely to reflect, to a small extent, the substituent effect on the complexation step.

Among the different solvents, water occupies a special position with a relatively small ρ -value. This is anticipated, since water is the solvent with the strongest interactions with the partial charges of the reacting system and the substituents. Substituent effects are usually larger in solvents that only weakly interact with these partial charges⁷⁰ and, hence, have maximal values in vacuum⁷¹. The ρ -values are of comparable magnitude in the different solvents, which makes it unlikely that there is a significant change in the extent of charge separation during the Diels-Alder reaction upon changing the solvent⁷².

The rate constants for the catalysed Diels-Alder reaction of **2.4g** with **2.5** (Table 2.3) demonstrate that the presence of the ionic group in the dienophile does not diminish the accelerating effect of water on the catalysed reaction. Comparison of these rate constants with those for the nonionic dienophiles even seems to indicate a modest extra aqueous rate enhancement of the reaction of **2.4g**. It is important to note here that no detailed information has been obtained about the exact structure of the catalytically active species in the organic solvents. For example, ion pairing is likely to occur in the organic solvents.

2.2.4 Variation of the catalyst

In the previous section efficient catalysis of the Diels-Alder reaction by copper(II)nitrate was encountered. Likewise, other bivalent metal ions that share the same row in the periodic system show catalytic activity. The effects of cobalt(II)nitrate, nickel(II)nitrate, copper(II)nitrate and zinc(II)nitrate



Scheme 2.6. Catalytic cycle for a Lewis-acid catalysed Diels-Alder reaction.

will be described in this section. Of the lanthanides, LaCl_3 , $\text{Yb}(\text{OTf})_3$ and $\text{Eu}(\text{NO}_3)_3$ have been tested, but these salts failed to reveal any catalytic activity with respect to the Diels-Alder reaction of **2.4**. Also Kobayashi's $\text{Sc}(\text{OTf})_3$ did not significantly promote this reaction. Likewise, salts of soft metals, PdCl_2 and $\text{Hg}(\text{NO}_3)_2$, have been tested, but these salts catalysed the hydration and oligomerisation of the diene rather than the desired Diels-Alder reaction.

The mechanism by which Lewis-acids can be expected to affect the rate of the Diels-Alder reaction in water is depicted in Scheme 2.6. The first step in the cycle comprises rapid and reversible coordination of the Lewis-acid to the dienophile, leading to a complex in which the dienophile is activated for reaction with the diene. After the irreversible Diels-Alder reaction, the product has to dissociate from the Lewis-acid in order to make the catalyst available for another cycle. The overall

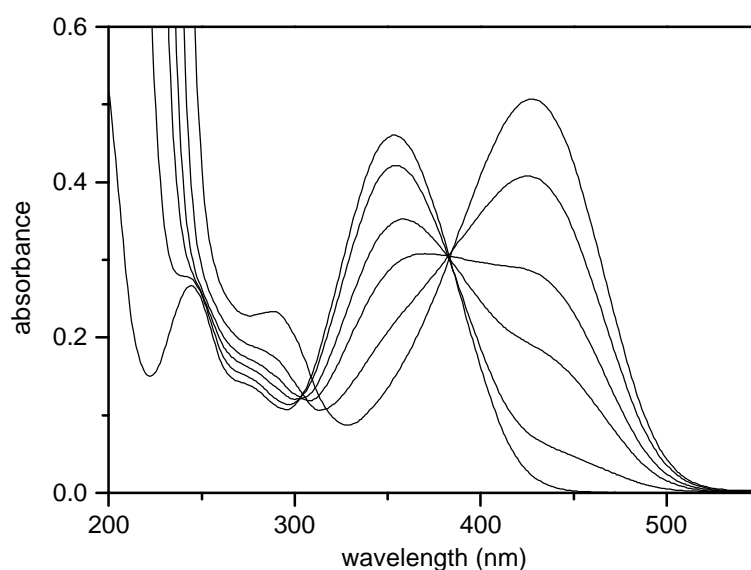


Figure 2.4. UV-vis absorption spectrum of **2.4e** in water at concentrations of copper(II)nitrate varying between 0 and 10 mM.

Table 2.5. Apparent second-order rate constants (k_{app}) for the catalysed Diels-Alder reaction between **1c** and **2**, equilibrium constants for complexation of **2.4c** to different Lewis-acids (K_a) and second-order rate constants for the reaction of these complexes with **2.5** (k_{cat}) in water at 2M ionic strength at 25°C.

Lewis-acid	k_{app} ($M^{-1}s^{-1}$) ^a	K_a (M^{-1})	k_{cat} ($M^{-1}s^{-1}$)
Co ²⁺	$4.53 \cdot 10^{-2}$	$1.17 \cdot 10^2$	$8.40 \cdot 10^{-2}$
Ni ²⁺	$8.26 \cdot 10^{-2}$	$6.86 \cdot 10^2$	$9.46 \cdot 10^{-2}$
Cu ²⁺	2.36	$1.16 \cdot 10^3$	2.56
Zn ²⁺	$4.29 \cdot 10^{-2}$	$7.28 \cdot 10^1$	$1.18 \cdot 10^{-1}$

^a For $[M^{2+}] = 10$ mM.

rate of the reaction is determined by K_a , k_{cat} , and K_d .

In the kinetic runs always a large excess of catalyst was used. Under these conditions K_d does not influence the apparent rate of the Diels-Alder reaction. Kinetic studies by UV-vis spectroscopy require a low concentration of the dienophile ($\sim 10^{-5}$ M). The use of only a catalytic amount of Lewis-acid will seriously hamper complexation of the dienophile because of the very low concentrations of *both* reaction partners under these conditions. The contributions of K_a and k_{cat} to the observed apparent rate constant have been determined by measuring k_{app} and K_a separately⁷³.

In determining the values of K_a use is made of the pronounced shift of the UV-vis absorption spectrum of **2.4** upon coordination to the catalytically active ions as is illustrated in Figure 2.4⁷⁴. The occurrence of an isosbestic point can be regarded as an indication that there are only two species in solution that contribute to the absorption spectrum: free and coordinated dienophile. The exact method of determination of the equilibrium constants is described extensively in reference 75 and is summarised in the experimental section. Since equilibrium constants and rate constants depend on the ionic strength, from this point onward, all measurements have been performed at constant ionic strength of 2.00 M using potassium nitrate as background electrolyte⁷⁶.

The equilibrium constants obtained using the metal-ion induced shift in the UV-vis absorption spectrum are in excellent agreement with the results of the Lineweaver-Burke analysis⁷⁷ of the rate constants at different catalyst concentrations. For the copper(II)ion catalysed reaction of **2.4a** with **2.5** the latter method gives a value for K_a of 432 versus 425 using the spectroscopic method.

From the equilibrium constant and the apparent rate constant, the rate constant for reaction of the metal-ion (M^{n+}) coordinated dienophile (k_{cat}) can be calculated using equation 2.2 (derived in Appendix 2.1).

$$k_{app} = \frac{K_a \cdot [M^{n+}]_t}{K_a \cdot [M^{n+}]_t + 1} k_{cat}$$

Equilibrium constants and second-order rate constants for Co²⁺, Ni²⁺, Cu²⁺ and Zn²⁺ catalysed of the reaction of **2.4c** with **2.5** in water at constant ionic strength (2.00 M KNO₃) are shown in Table 2.5.

Clearly, Cu²⁺ is the best catalyst with respect to both complexation and rate of reaction with **2.5**. The

trend observed in rate and equilibrium constants follows the empirical Irving-Williams order⁷⁸ $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} > \text{Zn}^{2+}$. This order is usually observed for equilibrium constants of binding processes and catalytic activities of these metal ions. This order can be accounted for using ligand field theory⁷⁹. The presence of a ligand in an octahedral arrangement around a metal ion causes a splitting in the energy level of the d-electrons of the metal into two new levels: t_{2g} and e_g (Figure 2.5). Depending on the occupation of the d-orbitals, this ligand field splitting results in a stabilisation of the complex. The extent of splitting is dependent on the ligand and follows the spectrochemical series. In general, bidentate ligands increase the splitting when compared to water. Hence, in the metal-**2.4** complexes ligand field splitting gives rise to an extra stabilisation as compared to the aquo complex. On the basis of these observations and considering the occupation of the t_{2g} and e_g levels for the different ions, ranging from d^7 to d^{10} , one would expect the order $\text{Co}^{2+} < \text{Ni}^{2+} > \text{Cu}^{2+} > \text{Zn}^{2+}$ with respect to the magnitude of K_a . However, copper(II) occupies a special position, which is a result of the Jahn-Teller effect. Of the three electrons in the e_g level, two are present in the d_{z^2} orbital and only one in the $d_{x^2-y^2}$ orbital. Consequently, those ligands that occupy the four equatorial sites experience repulsion due to only one d-electron and are bound more strongly than those that occupy the two axial positions, where they experience the two electrons of the d_{z^2} orbital. When combining the Jahn-Teller effect with ligand field theory, one arrives at the Irving-Williams series.

A quantitative correlation between rate and equilibrium constants for the different metal ions is absent. The observed rate enhancements are a result of catalysis by the metal ions and are clearly not a result of protonation of the pyridyl group, since the pH's of all solutions were within the region where the rate constant is independent of the pH (Figure 2.1).

Catalysis by the four metal ions was also compared with respect to their sensitivity towards substituents in the dienophile. To this end the equilibrium constants for complexation of **2.4a-g** to the four different ions were determined. The results are shown in Table 2.6.

Good to excellent Hammett plots were obtained using σ^+ substituent constants (see Figure 2.6). Surprisingly, literature examples of good Hammett correlations of stability constants are rare⁸⁰. The ρ -values are shown in Table 2.7.

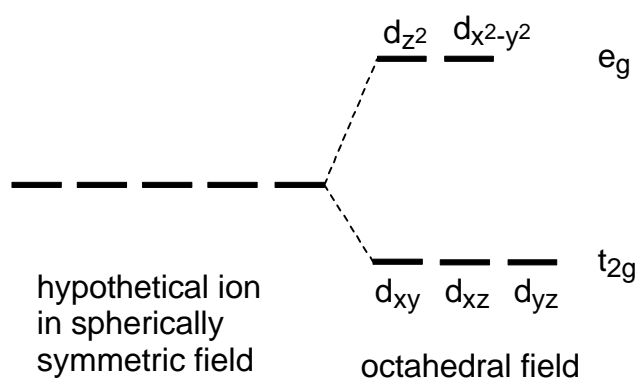


Figure 2.5. Splitting of the d energy level in an octahedral complex.

Table 2.6. Equilibrium constants from complexation of **2.4a**, **2.4b**, and **2.4d-g** to different metal ions (K_a) and second-order rate constants for the Diels-Alder reaction of these complexes with **2** (k_{cat}) in water at 2.00 M ionic strength and 25°C.

	Co^{2+}		Ni^{2+}		Cu^{2+}		Zn^{2+}	
	K_a	k_{cat}	K_a	k_{cat}	K_a	k_{cat}	K_a	k_{cat}
2.4a	86.9	$2.84 \cdot 10^{-1}$	$3.18 \cdot 10^2$	$5.69 \cdot 10^{-1}$	$4.25 \cdot 10^2$	11.1	34.5	$5.03 \cdot 10^{-1}$
2.4b	112	$1.02 \cdot 10^{-1}$	$5.79 \cdot 10^2$	$1.18 \cdot 10^{-1}$	$1.06 \cdot 10^3$	2.82	57.3	$1.22 \cdot 10^{-1}$
2.4d	127	$4.67 \cdot 10^{-2}$	$9.47 \cdot 10^2$	$4.61 \cdot 10^{-2}$	$1.55 \cdot 10^3$	1.36	88.1	$5.81 \cdot 10^{-2}$
2.4e	178	$2.11 \cdot 10^{-2}$	$1.50 \cdot 10^3$	$1.91 \cdot 10^{-2}$	$2.76 \cdot 10^3$	0.518	161	$2.48 \cdot 10^{-2}$
2.4f					$1.32 \cdot 10^3$	2.59		
2.4g	77	$1.64 \cdot 10^{-1}$	$5.04 \cdot 10^2$	$1.57 \cdot 10^{-1}$	$8.86 \cdot 10^2$	5.72	50.3	$2.17 \cdot 10^{-1}$

As anticipated, the complexation is characterised by negative ρ -values, indicating that the binding process is favoured by electron donating substituents. The order of the ρ -values for complexation of the different Lewis-acids again follows the Irving-Williams series.

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

So far the four metal ions have been compared with respect to their effect on (1) the equilibrium constant for complexation to **2.4c**, (2) the rate constant of the Diels-Alder reaction of the complexes with **2.5** and (3) the substituent effect on processes (1) and (2). We have tried to correlate these data with some physical parameters of the respective metal-ions. The second ionisation potential of the metal should, in principle, reflect its Lewis acidity. Furthermore the values for k_{cat} might be strongly influenced by the Lewis-acidity of the metal. A quantitative correlation between these two parameters

Table 2.7. Hammett ρ -values for complexation of **2.4a-e** to different Lewis-acids and for rate constants (k_{cat}) of the Diels-Alder reaction of **2.4a-e** with **2.5** catalysed by different Lewis-acids in water at 2.00 M ionic strength at 25°C.

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

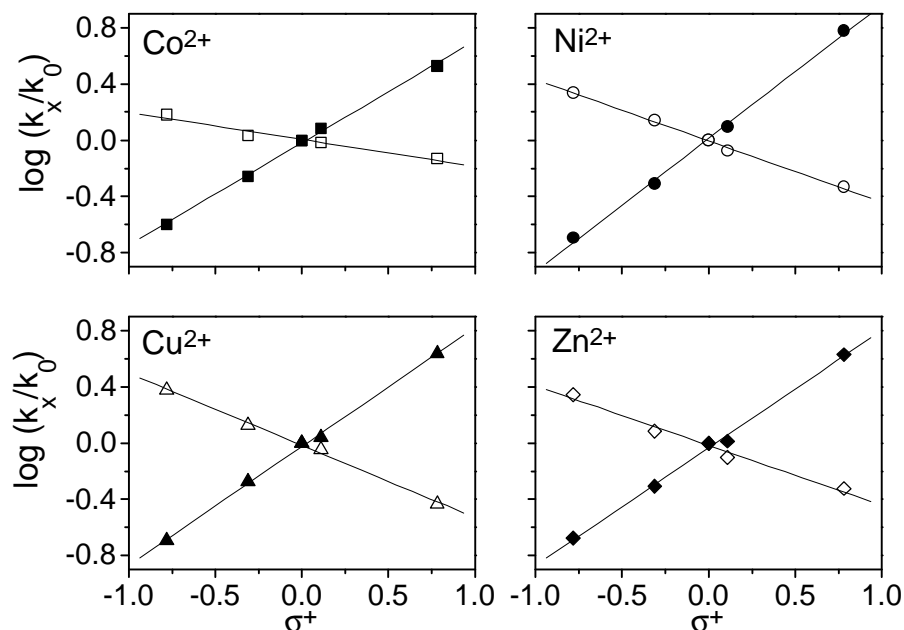


Figure 2.6. Hammett plots for the equilibrium constant K_a of binding of **2.4** to Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} (open symbols), and for the rate constants of reaction of the metal-ion - **2.4** complex with **2.5** (solid symbols).

is, however, not observed. Alternatively, the acidity of the hexaaquo metal cation can be taken as a measure of Lewis-acidity but this parameter did not exhibit a satisfactory correlation with the above data either.

2.2.5 Endo-exo selectivity

The reaction between **2.4** and **2.5** yields four products: two enantiomeric endo products and two enantiomeric exo products. In this section the effect of the solvent, the Lewis-acid and the substituents on the endo-exo selectivity are described. Chapter 3 will mainly focus on aspects dealing with the enantioselectivity of the reaction.

The endo and the exo isomer (Scheme 2.4) give rise to two different NMR-spectra with several peaks that are well separated. From the integration of those signals the endo-exo ratio can be determined. Measurement of the endo-exo ratio by GC was not successful, most likely because the adducts are subject to a retro-Diels-Alder reaction at elevated temperatures. Assignment of the signals to the different isomers was based on COSY and NOESY spectra. Interpretation of the spectra starts with the identification of the long-range coupling between $\text{H}7^s$ and $\text{H}2$, characteristic for norbornene systems⁸¹. The chemical shifts of the other protons can now easily be deduced. Discrimination between endo and exo adduct was subsequently based upon the following considerations. A NOE signal between $\text{H}3$ and a proton on the phenyl ring and a long-range coupling between $\text{H}2$ and a proton of the phenyl ring are both characteristic for the endo-isomer. Furthermore, the downfield shift

Table 2.8. Solvent effect on the endo-exo selectivity (% endo - % exo) of the uncatalysed and Cu²⁺-ion catalysed Diels-Alder reaction between **2.4c** and **2.5** at 25°C.

solvent	uncatalysed	10 mM Cu ²⁺
acetonitrile	67-33	94-6
ethanol	77-23	96-4
water	84-16	93-7
2,2,2-trifluoroethanol	87-13	

of H3 is larger in the endo isomer, where it experiences the influence of the nearby carbonyl-pyridyl group, than in the endo adduct, where H3 is situated next to the phenyl group. Comparison of the NMR data with literature data reported for the Diels-Alder adducts of cyclopentadiene and substituted cinnamic acids⁸¹ further supports the assignments.

The effects of the solvent on the endo-exo selectivity of the uncatalysed and Cu²⁺-catalysed reaction are shown in Table 2.8. For the uncatalysed reaction the endo isomer is preferred over the exo isomer. This tendency becomes even more pronounced in more polar and protic solvents, which is in good agreement with previous studies of the solvent effect on the selectivity of Diels-Alder reactions (see Section 1.2.3). For the Cu²⁺-catalyzed reaction the differences between the selectivities in the four solvents are much smaller. Obviously, water does not induce a higher selectivity in this case and there appears to be no indication for enforced hydrophobic interactions favouring the endo activated complex. Possibly, this effect is overwhelmed by differences in efficiency of activation by the Lewis-acid in the different solvents. It should be noted that the energy differences underlying the aqueous enhancement of endo-exo selectivity are in the range of 4 kJ/mole. In contrast, water lowers the activation energy for the Diels-Alder reaction of **2.4a** and **2.5** by 14 kJ/mol.

Table 2.9 shows the endo-exo selectivities for the Diels-Alder reaction between **2.4c** and **2.5** catalysed by Brønsted-acid and four different metal ions in water.

Copper is clearly the most selective metal-ion catalyst. Interestingly, proton catalysis also leads to high selectivities. This is a strong indication that selectivity in this catalysed Diels-Alder reaction does not result from steric interactions.

Table 2.9. Effect of different catalysts on the selectivity of the Diels-Alder reaction between **2.4c** and **2.5** in water at 25°C.

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

Table 2.10. Substituent effect on the selectivity of the Cu²⁺-catalysed reaction of **2.4** with **2.5** in water at 25°C.

dienophile	% endo - % exo
1a	88-12 ^a
1b	92-8 ^a
1c	93-7
1d	93-7
1e	93-7

^a The dienophile was not completely dissolved.

Table 2.10 shows the effect of substituents on the endo-exo ratio. Under homogeneous conditions there is hardly any substituent effect on the selectivity. Consequently the substituents must have equal effects on the Gibbs energies of the endo and the exo activated complex.

In summary, the effects of a number of important parameters on the catalysed reaction between **2.4** and **2.5** have been examined, representing the first detailed study of Lewis-acid catalysis of a Diels-Alder reaction in water. Crucial for the success of Lewis-acid catalysis of this reaction is the bidentate character of **2.4**. In Chapter 4 attempts to extend the scope of Lewis-acid catalysis of Diels-Alder reactions in water beyond the restriction to bidentate substrates will be presented.

2.3 Conclusions

The data presented in this chapter have clearly demonstrated that Lewis-acid catalysis of a Diels-Alder reaction in water is feasible. Relative to the reaction in acetonitrile, million-fold accelerations can be achieved by combining the beneficial effects of water and Lewis-acid catalysis. Unfortunately, these effects are not completely additive. The rate enhancing influence of water on the catalysed reaction is less pronounced than on the uncatalysed reaction. Most likely, this is a result of a reduced influence of hydrogen bonding in the aqueous rate enhancement of the catalysed reaction. In general, the solvent effect on the catalysed reaction is remarkably modest. Investigation of the substituent effects resulted in good Hammett correlations. The ρ -values obtained for the catalysed reactions are similar to those normally obtained for uncatalysed Diels-Alder reactions. This implies that the changes in charge separation during the activation process of the catalysed reaction are not significantly larger than the corresponding changes for the uncatalysed reaction. Of the different Lewis-acid catalysts that have been tested, the bivalent cobalt, nickel, copper and zinc ions showed the highest activity. The catalytic efficiency of these Lewis-acids followed the empirical Irving-Williams order: $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} \gg \text{Zn}^{2+}$. Study of the solvent effect on the endo-exo ratio of the uncatalysed reaction revealed the commonly observed increased selectivity for endo adduct in aqueous media. In contrast, the endo-exo selectivity of the Lewis-acid catalysed Diels-Alder reaction is not enhanced by water. Endo-exo ratios of the catalysed reaction were only moderately sensitive to

the solvent and to substituents in the dienophile.

Studies of the Diels-Alder reaction of the ionic dienophile **2.4g** have demonstrated that the aqueous acceleration of the uncatalysed reaction as well as the catalysed reaction is not significantly affected by the presence of the ionic group at a site remote from the reaction centre.

2.4 Experimental section

Materials

Cyclopentadiene (**2.5**) was prepared from its dimer (Merck-Schuchardt) immediately before use. Dimineralised water was distilled twice in a quartz distillation unit. Ethanol (Merck) was of the highest purity available. Acetonitrile (Janssen) was run over basic aluminium oxide prior to use. 2,2,2-Trifluoroethanol (Acros) was purified by distillation (bp 79°C). Co(NO₃)₂·6H₂O, Ni(NO₃)₂·6H₂O, Cu(NO₃)₂·3H₂O, Zn(NO₃)₂·4H₂O and KNO₃ were of the highest purity available. Substituted 3-phenyl-1-(2-pyridyl)-2-propene-ones (**2.4a-e**) were prepared by an aldol condensation of the corresponding substituted benzaldehyde with 2-acetylpyridine, following either of two modified literature procedures⁶⁴.

2.4a and 2.4b

To a stirred solution of 0.5 ml of 10% aqueous sodium hydroxide and 8.25 mmol of the appropriate aldehyde in 10 ml of ethanol, 8.25 mmol of 2-acetylpyridine was added dropwise during 2-3 hours. The temperature was kept at 0°C. After stirring for another 2 hours the reaction mixture was filtered, yielding almost pure solid **2.4a** (7.26 mmol, 88%) or **2.4b** (7.76 mmol, 94 %). After crystallisation from ethanol the melting points were recorded and the compounds were characterised by ¹H-NMR and mass spectroscopy. **2.4a**: mp 158.2-158.5°C (lit. 156°C⁸²; 154-5°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 7.55 (m,1H), 7.86 (d,2H), 7.91 (m,2H), 8.22 (m,1H), 8.27 (d,2H), 8.45 (d,1H), 8.77 (d,2H). Exact mass: calcd 254.069; found: 254.069. **2.4b**: mp 102.2-102.5°C (lit. 104°C⁸²; 91-92°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 7.39 (d,2H), 7.50 (m,1H), 7.67 (d,2H), 7.88 (m,2H), 8.19 (m,1H), 8.29 (d,1H), 8.75 (m,1H).

2.4c, 2.4d and 2.4e

17 mmol of 2-acetylpyridine and 16.5 mmol of the appropriate benzaldehyde were introduced into 100 ml of water at 0-5 °C. The mixture was shaken thoroughly in order to obtain a finely dispersed emulsion. 10 ml of a 10% sodium hydroxide solution was added. The mixture was again shaken and left overnight undisturbed at 4°C. The solution should not be stirred since this results in a phase separation and lower yields due to transport limitations. The product separated as an oil that solidified upon shaking. Filtration and washing with water gave the almost pure product in

satisfactory yields: **2.4c**: 95%, **2.4d**: 84%, **2.4e**: 96%. After crystallisation from ethanol the melting points were recorded and the compounds were characterised by ¹H-NMR. **2.4c**: mp 74.5-75.3 (lit. 74 °C⁸²; 71°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 7.46 (m,4H), 7.74 (m,2H), 7.86 (m,1H), 7.95 (d,1H), 8.20 (m,1H), 8.32 (d,1H), 8.75 (m,1H). **2.4d**: mp 84.8-85.3 (lit. 83°C⁸²), ¹H NMR (200 MHz, CDCl₃) δ 2.40 (s,3H), 7.23 (d,2H), 7.49 (m,1H), 7.64 (d,2H), 7.87 (m,1H), 7.93 (d,1H), 8.19 (m,1H), 8.27 (d,1H), 8.74 (m,1H). **2.4e**: mp 84.6-85.2 (lit. 84-85°C⁸²; 84°C⁸³), ¹H NMR (200 MHz, CDCl₃) δ 3.85 (s,3H), 6.93 (d,2H), 7.47 (m,1H), 7.69 (d,2H), 7.86 (m,1H), 7.92 (d,1H), 8.19 (d,1H), 8.19 (m,1H), 8.73 (m,1H).

2.4f and 2.4g

2.4f and **2.4g** have been prepared as outlined in Scheme 2.5. Yields were not optimised. *p*-(Bromomethyl)benzaldehyde (**2.8**) has been prepared by reaction of *p*-(bromomethyl)benzointrile (**2.7**, Acros) with diisobutylaluminium hydride following a literature procedure⁶⁵.

Sodium (p-oxomethylphenyl)methylsulfonate (2.9)

A suspension of 3.90 g (19.6 mmol) of *p*-(bromomethyl)benzaldehyde (**2.8**) and 4.00 g (31.7 mmol) of sodium sulfite in 40 ml of water was refluxed for two hours, after which a clear solution was obtained. The reaction mixture was cooled on an ice bath resulting in precipitation of some sodium sulfite. After filtration, the solvent was evaporated. Ethanol was added to the remaining solid and the suspension was refluxed for 10 minutes. After filtering the hot solution, the filtrate was allowed to cool down slowly to -18 °C whereupon sodium (p-oxomethylphenyl)methylsulfonate (**2.9**) separated as colourless crystals. The extraction procedure was repeated two more times, affording 2.29 g (10.3 mmol, 53%) of the desired product. ¹H-NMR (200 MHz, D₂O) δ(ppm) = 4.10 (s,2H); 7.44 (d,2H); 7.76 (d,2H); 9.75 (s,1H).

Sodium (4-(3-oxo-3-(2-pyridyl)-1-propenyl)phenyl)methylsulfonate (2.4f)

A solution of 75 ml of ethanol and 3.75 ml of a 10% solution of sodium hydroxide in water was cooled to 0 °C and 2.13 g (9.57 mmol) of sodium (p-oxomethylphenyl)methylsulfonate (**2.9**) and 1.28 g (10.6 mmol) of 2-acetylpyridine were added. The solution was stirred for 16 hours at 0°C and filtered affording 2.47 g (7.66 mmol, 80%) of crude **2.4f**. Crystallisation from methanol yielded 1.08 g (35%) of the desired product, mp 220 °C (decomposition). ¹H-NMR (200 MHz, D₂O) δ(ppm) = 4.00 (s,2H); 7.36 (d,2H); 7.55 (m,1H); 7.58 (d,2H); 7.61 (m,2H); 7.81 (m,2H); 8.43 (d,1H) Anal. Calcd for C₁₅H₁₂NO₄SNa : C, 55.4; H, 3.72; N, 4.31; S, 9.84; Na, 7.07. Found: C, 54.7; H, 3.74; N, 4.19; S, 9.41; Na, 6.97.

3-(p-(Bromomethyl)-phenyl)-1-(2-pyridyl)-2-propen-1-one (2.10)

A solution of 10 g of sodium hydroxide in 1.0 L of water was cooled to 0-5 °C. 5.95 g (49.2 mmol)

of 2-acetylpyridine and a solution of 7.25 g (36.4 mmol) p-(bromomethyl)benzaldehyde (**2.8**) dissolved in a minimal amount of ethanol were added. The resulting suspension was stirred for 48 hours at 0-5 °C. The product was filtered and washed extensively with water until the smell of the 2-acetylpyridine had disappeared. After drying at 50 °C under vacuum, 10.5 g (34.8 mmol, 96%) of 3-(p-(bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one (**2.10**) was obtained. ¹H NMR (200 Mhz, CDCl₃) δ(ppm) = 4.50 (s,2H); 7.42 (d,2H); 7.44 (m,1H); 7.70 (d,2H); 7.85 (m,1H); 7.91 (d,1H); 8.20 (d,1H); 8.31 (d,1H); 8.75 (d,1H).

(4-(3-Oxo-3-(2-pyridyl)-1-propenyl)phenyl)methyltrimethylammonium bromide (2.4g)

5.00 g (16.6 mmol) of 3-(p-(bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one (**2.10**) was suspended in 350 ml of dry ether under a nitrogen atmosphere. 20 ml of a 4.2 M solution of trimethylamine in ethanol (Fluka) was added. The reaction mixture was stirred for 24 hours at room temperature under a nitrogen atmosphere. Evaporation of the solvents and excess of trimethylamine afforded crude **2.4g** in quantitative yield. The very hygroscopic product can be crystallized from anhydrous 1-propanol. Removal of this solvent from the crystals is not possible by conventional methods. However, dissolving the product in water, filtration and subsequent freeze drying afforded 3.10 g (8.59 mmol, 52%) of **2.4g**, mp 212.5 °C (decomposition). ¹H-NMR (200 MHz, CDCl₃) δ(ppm) = 3.44 (s,9H); 5.16 (s,2H); 7.50 (m,1H); 7.75 (s,4H); 7.84 (d,1H); 7.85 (m,1H); 8.01 (d,1H); 8.31 (d,1H); 8.72 (d,1H). Anal. Calcd for C₁₈H₂₁N₂BrO: C, 60.0; H, 5.88; N, 7.78; Br, 21.92. Found: C, 59.8; H, 5.97; N, 7.58; Br, 21.77.

Kinetic measurements

All kinetic measurements were performed using UV-Vis spectroscopy (Perkin Elmer λ2, λ5 or λ12) monitoring the disappearance of the absorption of the dienophile at 25 ± 0.1 °C in the presence of a known excess of diene. Measurements were performed in cuvettes of 1 cm path length, initially containing only a solution of the dienophile. After equilibration, a 10-25 μl of a stock solution of cyclopentadiene in 1-propanol was added and the absorption was monitored. Two different methods were used to determine the second-order rate constants. The rates of the faster reactions (half-lives not more than a few hours) were determined by following the reaction during at least four half-lives. From the absorbance data, pseudo-first-order rate constants were obtained using a fitting-program. The rate constants of the slower reactions in organic solvents and the reactions with cyclopentadiene in water with half-lives of more than 15 minutes were determined using initial rate kinetics⁸⁴. Using a known excess of cyclopentadiene, the following expression was used to calculate the second-order rate constants:

$$k_2 = \frac{d(A_{2.4})}{dt} \cdot \frac{1}{d \cdot (e_{2.4} - e_{2.6}) \cdot [2.4]_0 \cdot [2.5]_0}$$

Herein d(A_{2.4})/dt is the slope of the plot of the absorption of the dienophile versus time during the first

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

Equilibrium constants

Measurements were performed employing a Perkin Elmer $\lambda 2$, 5 or 12 UV-Vis spectrophotometer at $25 \pm 0.1^\circ\text{C}$. Equilibrium constants were determined by measuring the extinction coefficient at a suitable wavelength of the partially complexed dienophile (ϵ_{obs}) as a function of the concentration of metal ion. The following expression can be derived⁸⁵:

$$\frac{[\text{M}^{n+}]}{\epsilon_{2.4} - \epsilon_{\text{obs}}} = \frac{1}{(\epsilon_{2.4} - \epsilon_{\text{compl}}) \cdot K_a} + \frac{[\text{M}^{n+}]}{\epsilon_{2.4} - \epsilon_{\text{compl}}}$$

After determining the extinction coefficient of the uncomplexed dienophile ($\epsilon_{2.4}$), $[\text{M}^{n+}]/(\epsilon_{2.4} - \epsilon_{\text{obs}})$ was plotted versus $[\text{M}^{n+}]$ yielding a straight line. The equilibrium constant now equals the ratio of the slope and the intercept of this line. Very accurate measurements of the extinction coefficients are a prerequisite for obtaining reliable equilibrium constants. Crucial in this respect were the choice of the wavelength and the choice of the appropriate metal-ion concentrations. The most accurate results were obtained at the wavelength of maximal difference between the extinction coefficients of uncomplexed and complexed dienophile. The metal-ion concentrations were chosen so as to cover the largest possible change in ϵ_{obs} with the smallest possible change in $[\text{M}^{2+}]$. Solutions of different $[\text{M}^{2+}]$ with total ionic strength of 2.00 M were prepared. KNO_3 was used as the background electrolyte. Extinction coefficients were determined by filling the cuvet with an accurately known volume of this solution and measuring the absorption after injection of 3-10 μl of a stock solution of the dienophile in 1-propanol. Typical concentration ranges were: [dienophile] = $6 \cdot 10^{-6}$ - $2 \cdot 10^{-5}$ M and $[\text{M}^{2+}]$ = $5 \cdot 10^{-3}$ - $2 \cdot 10^{-5}$ M. The reproducibility of the equilibrium constants varied between 5-10%.

Product analysis

Endo-exo product mixtures were isolated using the following procedure. A solution of cyclopentadiene (concentration $2 \cdot 10^{-3}$ M in water and 0.4 M in organic solvents) and the dienophile (concentration 1-5 mM) in the appropriate solvent, eventually containing a 0.01 M concentration of catalyst, was stirred at 25°C until the UV-absorption of the dienophile had disappeared. The reaction mixture (diluted with water in the case of the organic solvents) was extracted with ether. The ether layer was washed with water and dried over sodium sulfate. After the evaporation of the ether the

adducts were obtained in quantitative yields and almost invariably as oils. Only the reaction of **2.4c** and **2.5** in water with 10 mM HCl gave a white precipitate. The product mixtures were analysed with respect to their endo-exo ratio by $^1\text{H-NMR}$ spectroscopy. By repeating the extraction-drying procedure it was confirmed that the work-up procedure did not influence the endo-exo ratio of the isolated product mixture.

We have purified only the products of **2.4a** and **2.4c** by crystallisation from 1-propanol and ethanol, respectively. The purified products were still a mixture of endo and exo isomers. Elemental analyses of these compounds are given below. The Diels-Alder adducts of **2.4b**, **2.4d-g** were characterised by comparison of their NMR spectra with those of **2.4a** and **2.4c**. We will report here only the NMR data for the endo isomer, since the signals of the minor (7-12%) exo isomer partly coincide with the larger signals of the endo isomer and no attempts were made to separate the two. **2.6a**: Anal. ($\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3$) calcd. C: 71.22, H: 5.04, N: 8.75; found C: 70.82, H: 4.93, N: 8.66. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.65 (dd,1H), 1.99 (d,1H), 3.11 (d,1H), 3.52 (d,1H), 3.59 (s,1H), 4.46 (dd,1H), 5.85 (dd,1H), 6.47 (dd,1H), 7.21 (m,3H), 8.0 (m,5H), 8.6 (d,1H). **2.6b**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.61 (dd,1H), 2.00 (d,1H), 3.04 (d,1H), 3.40 (dd,1H), 3.54 (s,1H), 4.45 (dd,1H), 5.82 (dd,1H), 6.47 (dd,1H), 7.21 (m,5H), 7.45 (m,1H), 7.82 (m,1H), 7.99 (d,1H), 8.66 (d,1H). **2.6c**: Anal. ($\text{C}_{19}\text{H}_{17}\text{NO}$) calcd. C: 82.87, H: 6.23, N: 5.09; found C: 82.28, H: 6.24, N: 5.21. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.61 (dd,1H), 2.05 (d,1H), 3.07 (d,1H), 3.43 (dd,1H), 3.53 (s,1H), 4.51 (dd,1H), 5.81 (dd,1H), 6.47 (dd,1H), 7.21 (m,5H), 7.41 (m,1H), 7.80 (m,1H), 7.99 (m,1H), 8.65 (m,1H). **2.6d**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.60 (dd,1H), 2.07 (d,1H), 3.06 (d,1H), 3.42 (d,1H), 3.54 (s,1H), 4.53 (dd,1H), 5.83 (dd,1H), 6.49 (dd,1H), 7.09 (d,2H), 7.22 (d,2H), 7.43 (m,1H), 7.80 (m,1H), 8.00 (d,1H), 8.67 (d,1H). **2.6e**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.59 (dd,1H), 2.05 (d,1H), 3.02 (d,1H), 3.39 (d,1H), 3.52 (s,1H), 4.49 (dd,1H), 5.81 (dd,1H), 6.48 (dd,1H), 6.82 (d,2H), 7.23 (d,2H), 7.43 (m,1H), 7.79 (m,1H), 7.99 (d,1H), 8.67 (d,1H). **2.6f**: $^1\text{H NMR}$ (300 MHz, D_2O) δ 1.49 (dd,1H), 1.90 (d,1H), 2.98 (d,1H), 3.15 (d,1H), 3.27 (s,1H), 4.07 (s,2H), 4.25 (m,1H), 5.75 (m,1H), 6.44 (m,1H), 7.26 (s,4H), 7.55 (m,1H), 7.87 (m,2H), 8.52 (d,1H). **2.6g**: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.62 (dd,1H), 1.98 (d,1H), 3.07 (d,1H), 3.36 (s,9H), 3.43 (d,1H), 3.55 (2,1H), 4.45 (m,1H), 4.92 (s,2H), 5.82 (m,1H), 6.47 (m,1H), 7.36 (d,2H), 7.46 (m,1H), 7.52 (d,2H), 7.83 (dt,1H), 7.99 (d,1H), 8.66 (d,1H).

Appendix 2.1

In the presence of excess catalysts (M^{n+}) the rate of the Diels-Alder reaction of **2.4** with **2.5** is given by:

$$\frac{d[\mathbf{2.4}]_t}{dt} = k_0[\mathbf{2.4}]_f[\mathbf{2.5}] + k_{cat}[\mathbf{2.4} \cdot \text{M}^{n+}][\mathbf{2.5}] \quad (A1)$$

Herein k_0 is the second-order rate constant for the uncatalysed reaction and k_{cat} is the second-order rate constant for the reaction of the **2.4**-catalyst complex. $[\mathbf{2.4}]_f$ is the concentration of free dienophile

and $[2.4]_t$ is the total concentration of **2.4**.

An expression for the concentration of coordinated **2.4** (A4) can be obtained by combining the expression for the equilibrium constant K_a (A2) with the mass balance for **2.4** (A3).

$$K_a = \frac{[2.4 \cdot M^{n+}]}{[2.4]_f [M^{n+}]_f} \quad (A2)$$

$$[2.4]_t = [2.4]_f + [2.4 \cdot M^{n+}] \quad (A3)$$

$$[2.4 \cdot M^{n+}] = \frac{K_a \cdot [M^{n+}]_f}{K_a \cdot [M^{n+}]_f + 1} [2.4]_t \quad (A4)$$

Substitution of A4 in A1 gives:

$$\frac{d[2.4]_t}{dt} = k_0 [2.4]_f [2.5] + \frac{K_a \cdot [M^{n+}]_f}{K_a \cdot [M^{n+}]_f + 1} [2.4]_t [2.5] k_{cat} \quad (A5)$$

Under pseudo first-order conditions (excess **2.5**) k_{app} is given by:

$$k_{app} = \frac{1}{[2.5]} \cdot \frac{d[2.4]_t}{dt} \cdot \frac{1}{[2.4]_t} \quad (A6)$$

Substitution of A5 in A6 yields:

$$k_{app} = \frac{k_0 [2.4]_f}{[2.4]_t} + \frac{K_a \cdot [M^{n+}]_f}{K_a \cdot [M^{n+}]_f + 1} k_{cat} \quad (A7)$$

Since for the kinetic measurements a large excess of catalyst is used, the concentration of free catalyst $[M^{n+}]_f$ essentially equals the total concentration of catalyst. Moreover, since $k_0 \ll k_{cat}$ and under the conditions of the measurements the concentration of free **2.4** is small, the contribution of the uncatalysed reaction can be neglected and equation A7 simplifies to:

$$k_{app} = \frac{K_a \cdot [M^{n+}]_t}{K_a \cdot [M^{n+}]_t + 1} k_{cat} \quad (A8)$$

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Ligand Effects

Towards Enantioselective Lewis-Acid Catalysis in Water¹

In Chapter 2 the Lewis-acid catalysed Diels-Alder reaction between substituted 3-phenyl-1-(2-pyridyl)-2-propene-1-one dienophiles and cyclopentadiene was introduced. In this chapter the influence of ligands coordinated to the catalyst on the rate, on the endo-exo ratio and, for the first time, on the enantioselectivity of this reaction is described. None of the ligands that have been investigated have a significant effect on the endo-exo selectivity of the copper(II)-catalysed reaction in water. In contrast, ligands do influence the efficiency of this reaction. Most of the investigated ligands induce a decrease in the rate of the Diels-Alder reaction. Also the efficiency of binding of the dienophile to the catalyst tends to diminish in the presence of ligands. Interestingly, when aromatic²-amino acids are used, this situation reverses. These ligands enhance binding of the dienophile to the catalyst, most likely due to a specific ligand - dienophile interaction. When copper(II) ion is used as catalyst, this specific interaction can be used to induce enantioselectivity in the Diels-Alder reaction. Studies of the mechanism underlying this process are presented and, most importantly, it is shown that water as a solvent significantly enhances the enantioselectivity. To our knowledge, the results presented in this chapter provide the first example of enantioselective Lewis-acid catalysis of an organic reaction in water. This discovery opens the possibility of employing the knowledge and techniques from aqueous coordination chemistry in enantioselective catalysis, This work represents an interface of two disciplines hitherto not strongly connected.

3.1 Introduction

The influence of ligands² attached to catalytically active metal ions on the rate and particularly the enantioselectivity of organic reactions is one of the most extensively studied topics in homogeneous catalysis. Unfortunately, the approach is still largely based on trial and error. The latter is a consequence of the difficulties encountered in establishing the catalytic mechanism. Many catalytic processes are multistep sequences, involving many equilibria in which catalyst, starting material, intermediates, products and ligands are involved. Identification of the catalytically active species in complex reaction mixtures is notoriously difficult. Moreover, when dealing with selectivity, the small energy differences between the pathways leading to isomeric products are difficult to pinpoint and rationalise, let alone predict. This comment applies in particular to enantioselective catalysis.

When exclusively considering Lewis-acid catalysis, the literature on ligand effects can be divided into studies describing quantitatively the effect of ligands on rates and equilibria of the individual steps in the catalytic cycle on one hand, and studies focused on the enantioselectivity of the reaction on the other. Interestingly, in the majority of the former investigations, aqueous media are employed,

whereas studies dealing with enantioselective Lewis-acid catalysis have, so far, been strictly limited to organic solvents.

3.1.1 Studies of ligand effects on Lewis-acid catalysed reactions in water

Research on ligand effects in aqueous solution has mainly focused on two types of organic reactions: decarboxylation and hydrolysis reactions.

In section 2.1.1 the Lewis-acid catalysis of the decarboxylation of oxaloacetate was discussed. The mechanism of this reaction is outlined in entry 4 in Scheme 2.2. Between 1964 and 1977 a number of groups undertook systematic investigations of the effect of ligands on this reaction. The work was initiated by Rund and Plane³, who observed that a number of chelating ligands diminished the catalytic efficiency, with the exception of 1,10-phenanthroline, which induced a 16-fold increase in the rate of the manganese(II)-catalysed reaction. In the presence of 1,10-phenanthroline, the binding constant of the substrate to the metal ion was somewhat reduced, as expected on the basis of statistical arguments. According to Rund and Plane³ the increased catalytic efficiency in the presence of 1,10-phenanthroline resulted mainly from an increase in the rate constant for the decarboxylation of the catalyst-dimethyloxaloacetate complex. The presence of the 1,10-phenanthroline ligand was suggested to enhance the Lewis-acidity of the metal ion as a result of π -back donation from the metal to the ligand. Interestingly, when copper(II) or nickel(II) ions were used as catalysts, 1,10-phenanthroline induced only a two-fold acceleration⁴, whereas this ligand hardly affected the catalytic efficiency of zinc(II) and magnesium(II) ions⁵.

The effect of substituents in 1,10-phenanthrolines on the catalytic efficiency of the complex of this ligand and manganese(II) ion has been investigated⁶. The Hammett plots were not linear. Still, a trend of increasing catalytic efficiency with increasing donor character of the substituents was observed. This increase was explained in terms of an increased ligand-catalyst binding, leading to more efficient overlap of the π -orbitals of the ligand with those of the oxygens of the coordinated substrate, allowing for a more efficient delocalization of the negative charge that builds up during the activation process. The effect of 2,2'-bipyridine and 1,10-phenanthroline on the copper(II) ion-catalysed decarboxylation of oxaloacetate has been studied by Leong and Lister⁷. These aromatic ligands induce a two-fold increase in the equilibrium constant of binding of the substrate to the catalyst as compared to the aquo ion. The rate constant of the decarboxylation of the resulting complex was comparable to that of the aquo complex. Likewise, Raghavan and Leussing⁸ demonstrated that a substantial part of the acceleration of the observed rate of decarboxylation as induced by these ligands can be attributed to the suppression of the formation of inactive dinuclear oxaloacetate complexes.

There are a few documented examples of studies of ligand effects on hydrolysis reactions. Angelici et al.⁹ investigated the effect of a number of multidentate ligands on the copper(II) ion-catalysed hydrolysis of coordinated amino acid esters. The equilibrium constant for binding of the ester and the rate constant for the hydrolysis of the resulting complex both decrease in the presence of ligands. Similar conclusions have been reached by Hay and Morris, who studied the effect of ethylenediamine

on the copper(II) and mercury(II) ion-catalysed hydrolysis of 2,3-diaminopropionic acid¹⁰. These authors also studied the copper(II) and nickel(II) ion-catalysed hydrolysis of coordinated L-histidine methyl ester in the presence of L- and D-histidine as a ligand. The nickel catalysed reaction showed a modest degree of diastereoselectivity¹¹. Schneider et al.¹² studied the effect of ligands on the lanthanide-ion catalysed hydrolysis of phosphoric acid diesters. All employed ligands reduced the catalytic efficiency.

In summary, ligands tend to diminish the affinity of the substrate for the Lewis-acid catalyst as well as the extent of activation by this catalyst, once the ternary complex is formed. Only a few examples of ligand-accelerated catalysis¹³ have been described.

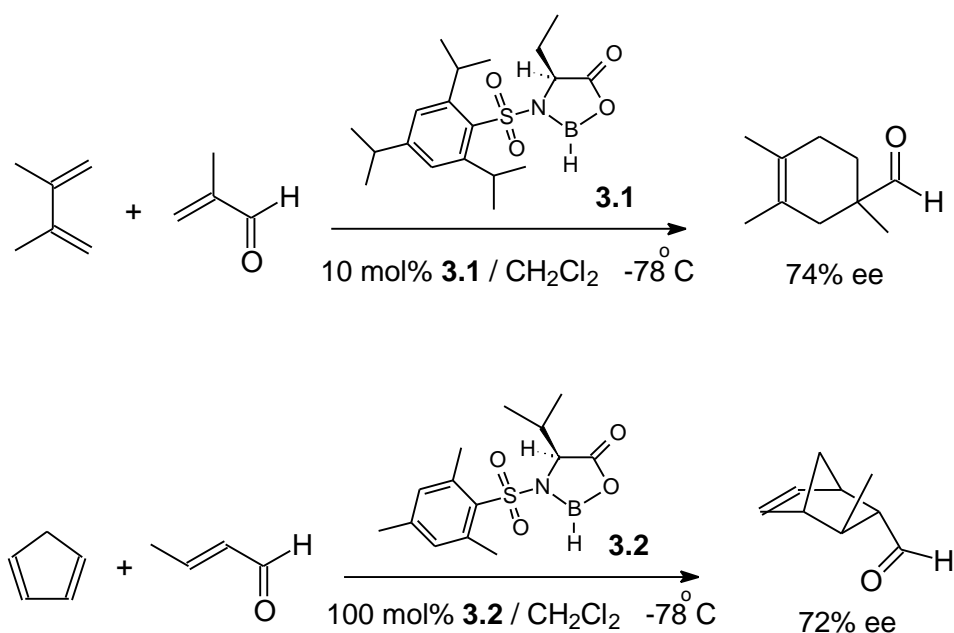
3.1.2 Enantioselective Lewis-acid catalysis

Chirality (handedness) is older than life on this planet¹⁴. Still it was not until 1848 when Pasteur manually separated enantiomeric crystals that chirality in chemistry was first appreciated¹⁵. The independent work of Van 't Hoff¹⁶ and Le Bel¹⁷ revealed the molecular origin behind this phenomenon.

Of the molecules that exist in two enantiomeric forms, nature generally uses only one. Proteins, for instance, normally are built from the L enantiomers of α -amino acids. This feature has severe implications for synthetic organic chemists when preparing compounds that are designed to interact with living organisms. Synthesis of chiral compounds, in the absence of a chiral source, yields equal amounts of both enantiomers, which have, with regard to achiral operations, the same physical properties. However, their interaction with biological systems can differ dramatically. Asparagine, for instance, is a chiral molecule of which the R enantiomer is used as artificial sweetener, whereas the S form tastes bitter. Another example, with horrible consequences, is thalidomide, commercialised as Softenon, of which the R form has a desired effect as tranquiliser, whereas the S enantiomer produced severe foetal deformities¹⁸.

Clearly, there is a need for techniques which provide access to enantiomerically pure compounds. There are a number of methods by which this goal can be achieved¹⁹. One can start from naturally occurring enantiomerically pure compounds (the chiral pool). Alternatively, racemic mixtures can be separated via kinetic resolutions or via conversion into diastereomers which can be separated by crystallisation. Finally, enantiomerically pure compounds can be obtained through asymmetric synthesis. One possibility is the use of chiral auxiliaries derived from the chiral pool. The most elegant method, however, is enantioselective catalysis. In this method only a catalytic quantity of enantiomerically pure material suffices to convert achiral starting materials into, ideally, enantiomerically pure products. This approach has found application in a large number of organic reactions²⁰.

The first example of enantioselective catalysis of a Diels-Alder reaction was reported in 1979²¹. Since then, an extensive set of successful chiral Lewis-acid catalysts has been prepared. Some selected examples will be presented here together with their mechanistic interpretation. For a more complete

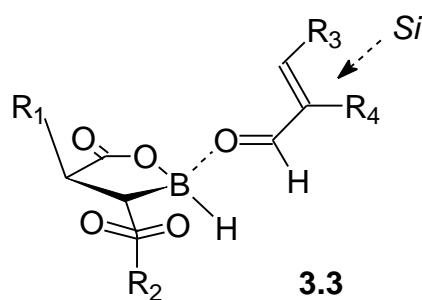


Scheme 3.1.

overview the reader is referred to a number of review articles and monographs^{20,22}.

Independently, the groups of Yamamoto²³ and Helmchen²⁴ reported the induction of enantioselectivity in a number of Diels-Alder reactions by chiral γ -amino acid derived oxazaborolidine catalysts **3.1** and **3.2**, respectively (Scheme 3.1). Helmchen et al.²⁴ suggested transition state assembly **3.3** (Scheme 3.2) to account for the observed enantioselectivity. The authors rationalised the mechanism underlying enantioselectivity as follows: R_1 directs the bulk of R_2 towards the opposite face of the ring. The R_2 -group, in turn, controls the configuration at the boron centre. On the basis of experimental and theoretical work on related systems it was assumed that the enal coordinates to the boron centre through its lone pair syn to the aldehyde proton. The cisoid conformation of the enal was assumed on the basis of the results of a computer simulation. Attack of the diene from the *Si* face (see Figure 3.1) leads to the enantiomer that is obtained in excess.

Interestingly, Corey et al.²⁵, employing a similar tryptophan-derived catalyst (**3.4**), observed a 99% enantiomeric excess²⁶ (ee) in the Diels-Alder reaction of 2-bromoacrolein with cyclopentadiene



Scheme 3.2.

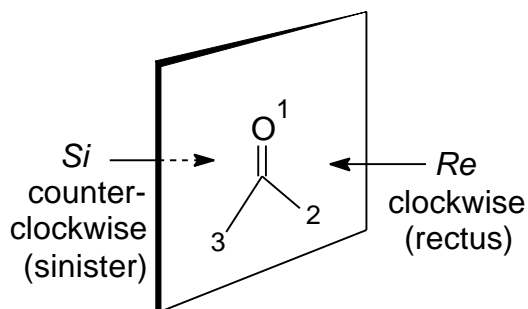
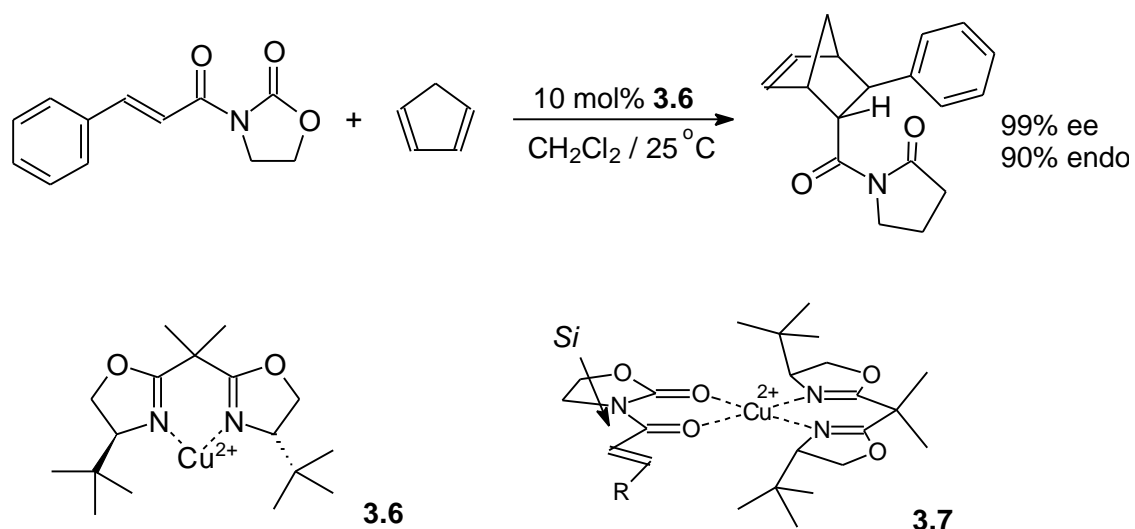


Figure 3.1. Definition of the Re and Si face of a prochiral ketone.

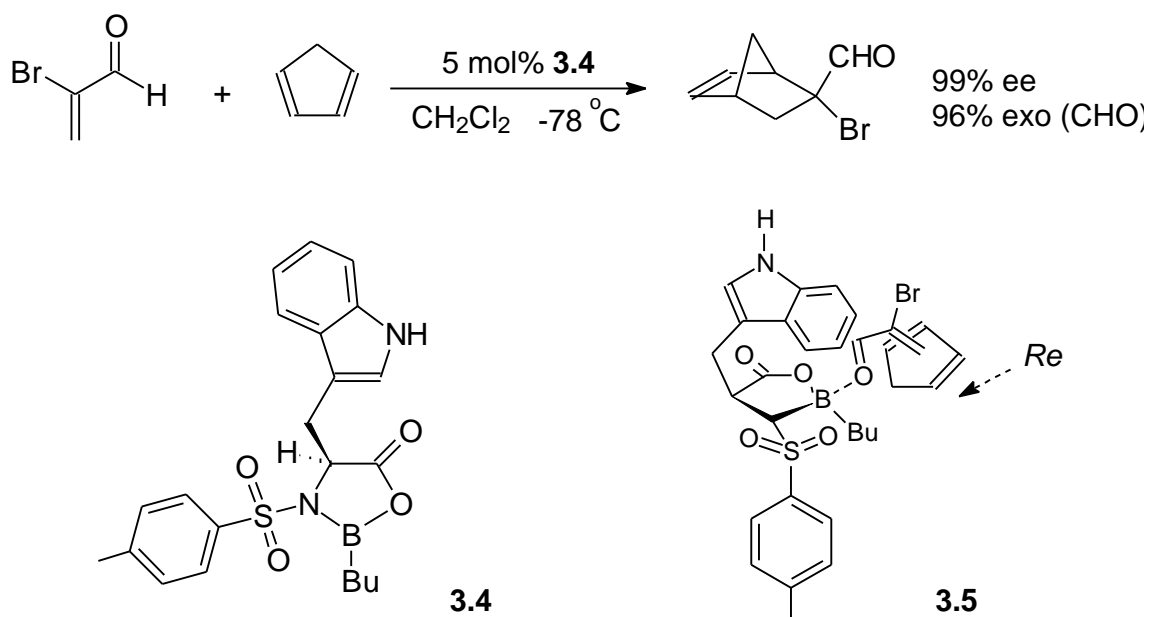
(Scheme 3.3) . Surprisingly, the major enantiomer in this reaction has the R configuration, whereas the major product of the same reaction using catalyst **3.1** or **3.2** has the S configuration. An attractive interaction between the indole ring of the catalyst and the coordinated dienophile has been held responsible for this remarkable difference. A number of experimental observations support this suggestion²⁵. At 210 K a bright orange-red colour appears for the complex of 2-methylacrolein with a methylated derivative of **3.4**, which has been ascribed to a charge transfer between the π -donor indole ring and the coordinated aldehyde. Corey and co-workers²⁵ suggested transition state assembly **3.5** to account for these observations. Note the subtle difference in the orientation of the enal with respect to the oxazaborolidine ring in **3.5** as compared to **3.3**. Rotation of the boron - enal oxygen bond suffices to transform the one into the other. Interestingly, substituting the indole ring in **3.4** for a naphthalene group results in a diminished enantiomeric excess of 75%, whereas upon replacement of the indole ring by a phenyl, cyclohexyl or propyl group, the Diels-Alder adduct is



Scheme 3.4.

obtained in about 30% ee, but now of the other enantiomer²⁵. Seerden et al. employed a benzyl ether substituted L-tyrosine derived catalyst, which induced 81 % ee of the same enantiomer that is formed in excess by the tryptophan derived catalyst²⁷.

Evans and co-workers²⁸ investigated the effect of a number of C_2 -symmetric bis(oxazoline) ligands on the copper(II)-catalysed Diels-Alder reaction of an N-acyloxazolidinone with cyclopentadiene. Enantiomeric excesses of up to 99% have been reported (Scheme 3.4). Evans et al.²⁸ suggested transition state assembly **3.7**, with a square planar coordination environment around the central copper ion. In this scheme the dienophile should be coordinated predominantly in an cisoid fashion in

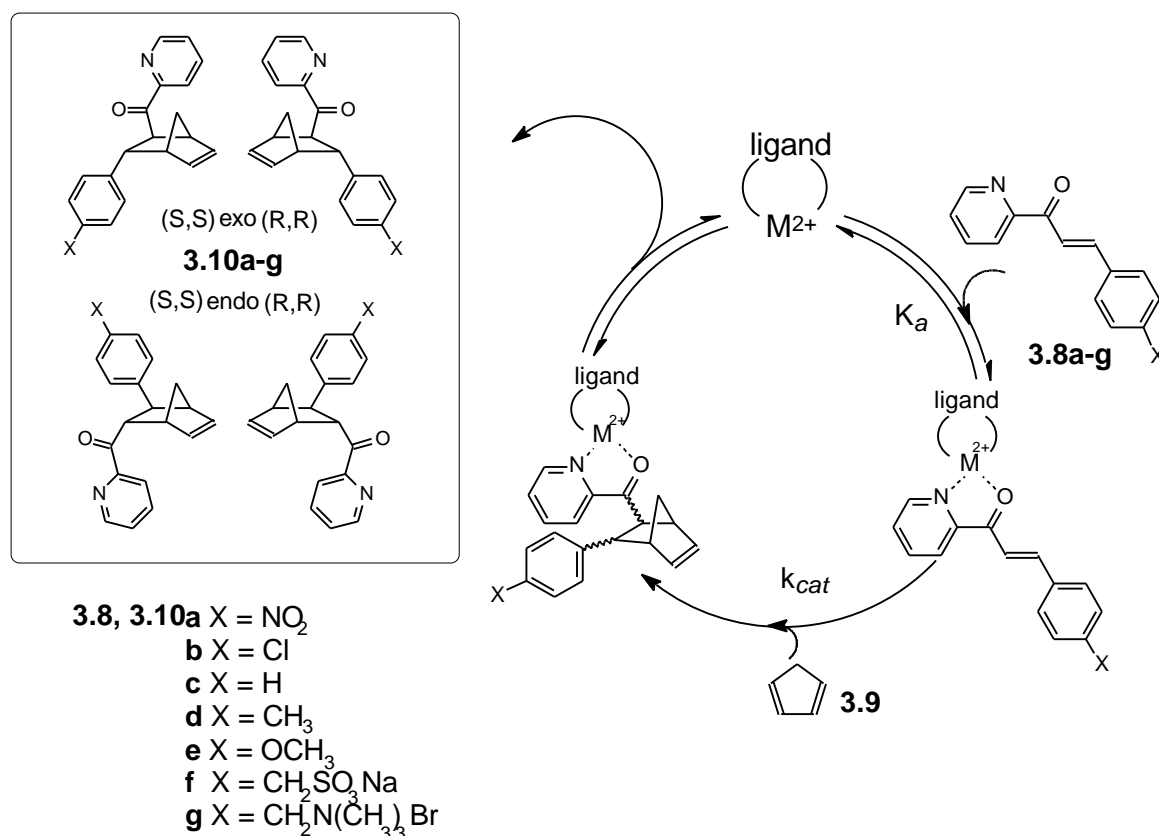


Scheme 3.3.

order to arrive at the enantiomer that is obtained in excess.

Recently Desimoni et al.²⁹ used the same bis(oxazoline) ligand in the magnesium(II) catalysed Diels-Alder reaction of the N-acyloxazolidinone depicted in Scheme 3.4. In dichloromethane a modest preference was observed for the formation of the S-enantiomer. Interestingly, upon addition of two equivalents of water, the R-enantiomer was obtained in excess. This remarkable observation was interpreted in terms of a change from tetrahedral to octahedral coordination upon the introduction of the strongly coordinating water molecules.

In summary, these examples illustrate the extreme sensitivity of the enantioselectivity towards subtle changes in geometry of the substrate-catalyst complex such as coordination environment, modes of binding of the substrate and the cisoid - transoid equilibrium of the coordinated dienophile. A change in any of these parameters is usually reflected in a change of the major enantiomer from R to S or visa-versa. The minor energy differences that distinguish preferred from averred geometries are usually hard to predict. The fact that all possible geometries have their own unique reactivities even further hampers rationalisation of enantioselective catalysis.



Scheme 3.5.

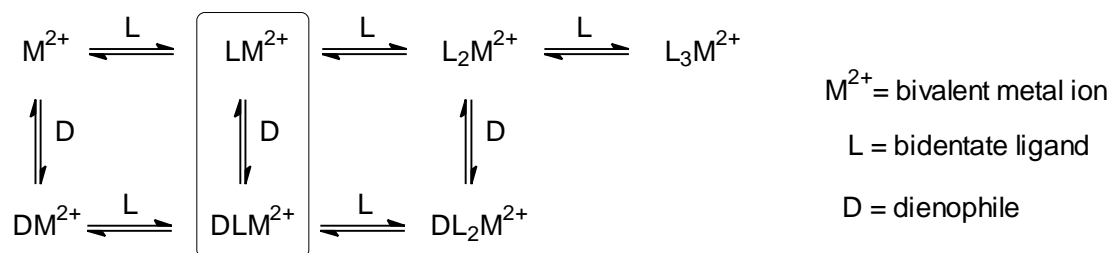
3.2 Results and discussion

In Chapter 2 the Diels-Alder reaction between substituted 3-phenyl-1-(2-pyridyl)-2-propene-1-ones (**3.8a-g**) and cyclopentadiene (**3.9**) was described. It was demonstrated that Lewis-acid catalysis of this reaction can lead to impressive accelerations, particularly in aqueous media. In this chapter the effects of ligands attached to the catalyst are described. Ligand effects on the kinetics of the Diels-Alder reaction can be separated into influences on the equilibrium constant for binding of the dienophile to the catalyst (K_a) as well as influences on the rate constant for reaction of the complex with cyclopentadiene (k_{cat}) (Scheme 3.5). Also the influence of ligands on the endo-exo selectivity are examined. Finally, and perhaps most interestingly, studies aimed at enantioselective catalysis are presented, resulting in the first example of enantioselective Lewis-acid catalysis of an organic transformation in water.

3.2.1 Effects of achiral ligands

At the outset of a systematic study of ligand effects on the Lewis-acid catalysed Diels-Alder reaction of **3.8** with **3.9** one can choose from an extensive set of ligands. The initial choice was inspired by the beneficial effect that had been reported for aromatic amine ligands in the transition metal ion-catalysed decarboxylation of oxaloacetate (see Section 3.1.1) and derivatives thereof. Particularly 1,10-phenanthroline (see Table 3.1) was observed to increase the catalytic efficiency. Consequently, the effect of this ligand was investigated. For comparison purposes a number of other diamines varying in the size of their aromatic system (2,2'-bipyridine, 2-aminomethylpyridine and ethylenediamine) were included. All these ligands are characterised by an extremely high affinity for the catalyst ions. The equilibrium constants for binding of these compound to the catalytically active metal ions are at least three orders of magnitude higher than those for binding of the dienophiles³⁰.

In Chapter 2 it has been demonstrated that Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} exhibit pronounced catalytic activity toward the Diels-Alder reaction under investigation. In aqueous solution these ions generally form octahedral complexes. Copper(II) ion occupies a special position among these catalysts. Due to the Jahn-Teller effect (see Section 2.2.4), coordination to the four equatorial sites is stronger than to

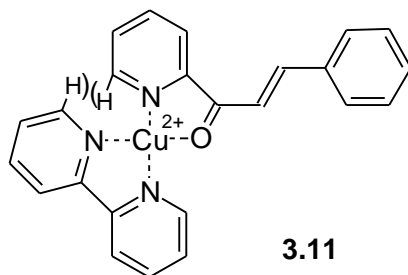


Scheme 3.6.

the two remaining axial positions. Consequently, in the absence of special geometrical constraints in the ligands, four-coordinated copper(II) complexes are generally characterised by a square planar geometry. In contrast, there is usually no intrinsic preference for axial over equatorial coordination in Co^{2+} , Ni^{2+} and Zn^{2+} complexes. In view of the higher catalytic activity of Ni^{2+} and particularly Cu^{2+} ions, research into the effect of ligands has focused on catalysis by these two ions.

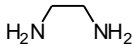
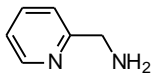
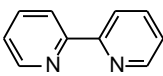
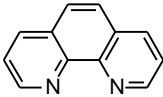
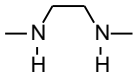
Measurements of rate and equilibrium constants that determine the efficiency of the catalysed Diels-Alder reaction were performed using UV-vis techniques, as described in Chapter 2. These techniques require the use of an excess of catalyst, resulting in catalyst concentrations typically in the order of several millimolar. Under these conditions it is assumed that there are only two catalyst species in solution: the ligand-metal ion complex and the ternary ligand-metal ion-dienophile complex (Scheme 3.6). This assumption greatly simplifies the analysis, but is essentially not correct. Inevitably, there is also a finite concentration of metal aquo ion as well as some metal ion coordinating two or three ligands. The relative amounts of these species are strongly pH-dependent, which even further complicates the analysis. Complete quantitative assessment of the composition of these mixtures is possible³¹ but, in view of the explorative character of the research, was not pursued.

Table 3.1 summarises the influence of the diamine ligands on the equilibrium constant for binding of **3.8c** to the ligand-metal ion complex (K_a) and the second-order rate constant for reaction of the ternary complex (k_{cat}) (Scheme 3.5) with diene **3.9**.



Scheme 3.7.

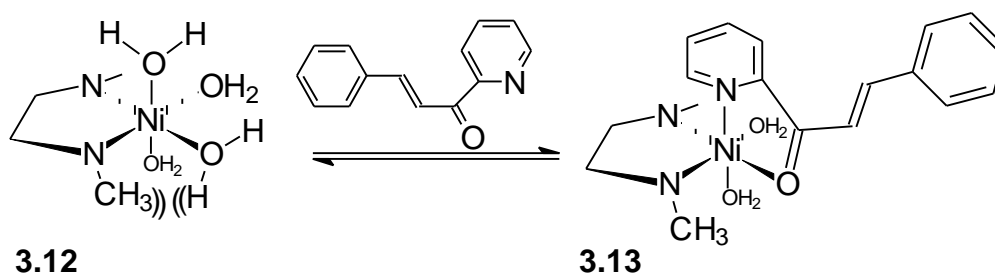
Table 3.1 Influence of several diamine ligands on the equilibrium constant for binding of **3.8c** to the ligand-metal ion complex (K_a) and the second-order rate constant for reaction of the ternary complex (k_{cat}) with diene **3.9**^a.

ligand		eq. ^b	Cu ²⁺		Ni ²⁺	
structure	name		K_a (M ⁻¹)	k_{cat} (M ⁻¹ s ⁻¹)	K_a (M ⁻¹)	k_{cat} (M ⁻¹ s ⁻¹)
"H ₂ O"			1.16 $\times 10^3$	2.56	686	9.46 $\times 10^{-2}$
	ethylenediamine	1	4.58 $\times 10^2$	2.91	437	9.76 $\times 10^{-2}$
		2			136	8.73 $\times 10^{-2}$
	2-(aminomethyl)pyridine	1	3.74 $\times 10^2$	3.12		
	2,2'-bipyridine	1	1.78 $\times 10^2$	0.838	519	7.43 $\times 10^{-2}$
		2			337	1.02 $\times 10^{-1}$
	1,10-phenanthroline	1	1.78 $\times 10^2$	0.626	565	8.20 $\times 10^{-2}$
		2			372	9.03 $\times 10^{-2}$
	N,N'-dimethyl ethylenediamine	1	4.12 $\times 10^2$	2.46	800	9.75 $\times 10^{-2}$
		2			693	8.19 $\times 10^{-2}$

^a All measurements were performed at constant ionic strength (2.00 M using KNO₃ as background electrolyte) and at pH 7-8. ^b Ligand-catalyst ratio.

From the data in Table 3.1 it can be concluded that binding of **3.8c** to copper(II) ions is invariably hampered by the presence of the diamine ligands. On a simple statistical basis, a reduction of the equilibrium constant can be anticipated, since the ligand can be expected to block coordination sites on the metal ion. For square planar coordinated copper(II) ions, this effect will cause bidentate ligands to reduce K_a by 50%. The effects of ethylenediamine and dimethylethylenediamine can be explained on this statistical basis. 2,2'-Bipyridine and 1,10-phenanthroline, on the other hand, show a further reduction of the equilibrium constant for binding of the dienophile. An additional steric repulsion between the β -pyridine proton of the dienophile and an α -pyridine proton of the ligand might well be operative (Scheme 3.7). Note that in the ternary complex containing the 2-(aminomethyl)pyridine ligand, this interaction can be avoided by positioning the pyridine ring of the dienophile trans with respect to the ligand pyridine ring.

Interestingly, the rate constants for Diels-Alder reaction of the ternary complexes with **3.9** are remarkably similar. Only with 2,2'-bipyridine and 1,10-phenanthroline as ligands, a significant change in reactivity is observed. It might well be that the inability of these complexes to adopt a planar geometry hampers the interaction between the copper ion and the dienophile, resulting in a decrease of the rate of the catalysed Diels-Alder reaction.



Scheme 3.8.

When Ni^{2+} ion is used, a simple statistical argument predicts a bidentate ligand to reduce the equilibrium constant for binding of the dienophile by one third, if one equivalent of ligand is added, and by two thirds for two equivalents. When using ethylenediamine and 2,2'-bipyridine as ligands, this trend is observed. However, with *N,N'*-dimethylethylenediamine a different behaviour is encountered. One equivalent of this ligand *raises* K_a above the value for nickel aquo ion. It might well be that the methyl groups of the ligand hinder coordination of the water molecules in the two remaining equatorial positions of the complex, facilitating their displacement by the dienophile (Scheme 3.8). Note that the steric repulsion between the coordinated water molecules and the ligand methyl groups is likely to occur also for the corresponding copper complex. However, in that case, the pyridine ring of the dienophile, upon replacing a water molecule, will experience a similar repulsion, whereas in the nickel complex, this ring is free to occupy an axial position. The difference between the effects of 2,2'-bipyridine on the nickel and copper complexes can be explained using a similar argument. The availability of the axial positions in the nickel coordination sphere enables adoption of geometries where ligand and dienophile are in different planes, so that a steric clash of the pyridine π -hydrogens is avoided.

The rate of the Ni^{2+} -catalysed Diels-Alder reaction is barely sensitive to the presence of ligands. Apparently no significant effect due to π -back donation is observed, in contrast to the effect of aromatic diamines on the metal-ion catalysed decarboxylation reaction of oxaloacetate (see Section 3.1.1).

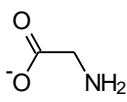
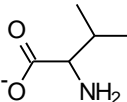
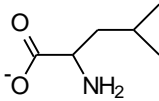
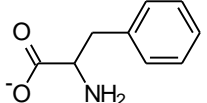
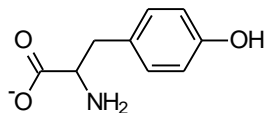
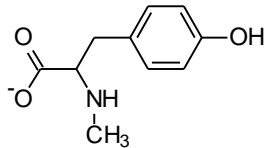
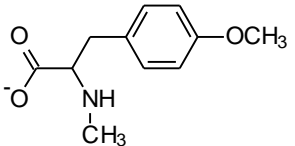
In summary, for the most active of catalysts, the copper(II) ion, the diamine ligands that were investigated seriously hamper catalysis mainly by decreasing the efficiency of coordination of the dienophile. With exception of the somewhat deviant behaviour of *N,N'*-dimethylethylenediamine, this conclusion also applies to catalysis by Ni^{2+} ions. Hence, significant ligand-accelerated catalysis using the diamine ligands appears not to be feasible.

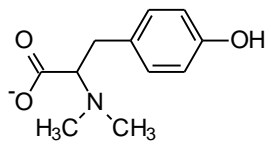
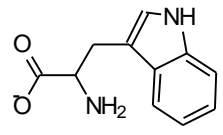
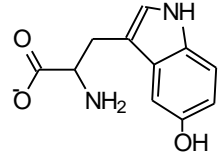
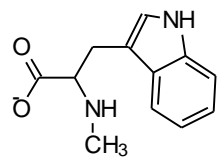
3.2.2 Effects of *L*- α -amino acid ligands - Stepping on the tail of enantioselectivity

The naturally occurring α -amino acids form a class of readily available strongly coordinating ligands, which exhibit broad structural variation. Moreover, their availability in enantiomerically pure form offers opportunities for enantioselective catalysis. Some derivatives of these compounds have been

used successfully as chiral units in enantioselective catalysis in organic solvents (see Section 3.2.2). At neutral, or slightly acidic pH, α -amino acids tend to coordinate to transition metal ions in the deprotonated form, resulting in the formation of a five-membered ring, which is usually flat³². The effect of a series of α -amino acids on the Diels-Alder reaction of **3.8** with **3.9** has been investigated. The results are shown in Table 3.2.

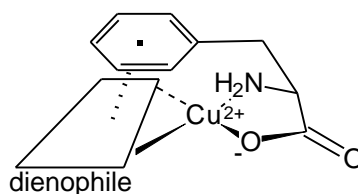
Table 3.2. Influence of several α -amino acid ligands on the equilibrium constant for binding of **3.8c** to the ligand-Cu²⁺ complex (K_a) and the second-order rate constant for reaction of this ternary complex with diene **3.9** (k_{cat})^a and the enantioselectivity of this reaction in water^b.

ligand		K_a	k_{cat}	$ee^{c,26}$
structure	name	(M ⁻¹)	(M ⁻¹ s ⁻¹)	(%)
"H ₂ O"		1.16 $\times 10^3$	2.56	-
	glycine	6.29 $\times 10^2$	1.89	-
	L-valine	5.71 $\times 10^2$	1.90	3 ^d
	L-leucine	5.14 $\times 10^2$	2.01	3 ^d
	L-phenylalanine	8.66 $\times 10^2$	2.01	17
	L-tyrosine	1.40 $\times 10^3$	1.68	36
	N-methyl-L-tyrosine	2.45 $\times 10^3$	2.07	74
	N-methyl-p-methoxy-L-phenylalanine	2.04 $\times 10^3$	2.83	67

	N,N-dimethyl-L-tyrosine	$1.66 \cdot 10^3$	2.92	73
	L-tryptophan	$3.02 \cdot 10^3$	1.44	25 ^d
	5-hydroxy-L-tryptophan	$4.89 \cdot 10^3$	1.15	29
	L-abrine	$5.05 \cdot 10^3$	1.47	74

^a All measurements were performed at constant ionic strength (2.00 M using KNO₃) as background electrolyte) and at pH 4.6-5.2. ^b 10 mol% Cu(NO₃)₂; 17.5 mol% ligand; conditions as outlined in the experimental section. ^c Only the results for the major (>90%) endo isomer of the Diels-Alder adduct are shown. ^d 250 mole % of catalyst was used.

The aliphatic α -amino acids induce a reduction of the equilibrium constant for binding of the dienophile to the copper ion by roughly 50 %, as anticipated on the basis of statistics. However, when L-phenylalanine is used as ligand, this reduction is significantly less pronounced. For L-tyrosine, L-tryptophan and derivatives thereof, the equilibrium constant is even *larger* than that of the copper aquo ion. Compared to the most bulky of the aliphatic α -amino acids, L-leucine ($\Delta G_{\text{compl}}^{\circ} = -15.5$ kJ/mole), L-abrine ($\Delta G_{\text{compl}}^{\circ} = -21.1$ kJ/mole) enhances the affinity of the catalyst for the dienophile by 5.6 kJ/mol. This enhancement cannot be attributed to a steric effect, since an increase of steric bulk (going from L-glycine, to L-valine, to L-leucine) leads to a modest reduction of K_{a} . Most likely, a specific interaction between the aromatic system of the α -amino acid ligand and that of the coordinated dienophile (arene-arene interaction³³) is responsible for the enhanced stability of the ternary complex (see Scheme 3.9). This type of ligand - ligand interaction is well documented. The most relevant literature on this topic is summarised in Section 3.2.3.



Scheme 3.9.

From the data in Table 3.2 it is apparent that almost all β -amino acid ligands induce a modest deceleration of the Diels-Alder reaction of **3.8c** with **3.9**. These ligands have a somewhat larger influence on the rate of the reaction than most of the diamines in Table 3.1. Most likely, this difference can be ascribed to the fact that the β -amino acids coordinate in the deprotonated form, whereas the diamine ligands are neutral. The negatively charged amino acid oxygen in the coordination sphere of the catalyst reduces its Lewis acidity. Fortunately, this effect is modest and for N-methyl-p-methoxy-L-phenylalanine and N,N-dimethyl-L-tyrosine even absent, so that under suitable conditions, ligand-accelerated catalysis by aromatic β -amino acids seems feasible.

3.2.3 Ligand - ligand interactions in ternary complexes - a literature survey

The enhanced stability of ternary complexes due to ligand - ligand interactions has been reported for an extensive set of complexes. Granot³⁴ studied the complexes of catecholamines and divalent metal ion-coordinated ATP. From an analysis of the Gibbs energy, enthalpy and entropy changes upon complexation, he suggested the occurrence of ring stacking, predominantly driven by London dispersion interactions. Similar ligand-ligand interactions have been reported to occur in mixed ligand ATP - bivalent metal ion - 2,2'-bipyridine³⁵, flavin mononucleotide - Cu²⁺ - 1,10-phenanthroline³⁶ as well as ATP - bivalent metal ion - β -amino-acid complexes³⁷. Kim and Martin³⁸ investigated the interaction of the aromatic ring of phenylalanine and the aliphatic side chain of monodentate amines in square planar palladium(II) complexes. This interaction has been reported to stabilise the ternary complexes by maximally 2.3 kJ/mole. Attachment of a phenyl ring to the amine has been observed to increase the stabilisation by 0.3-1.5 kJ/mole.

Similar ligand-ligand interactions have been reported for a large number of ternary β -amino acid complexes, built up of two different amino acids. A compilation of 72 examples is presented in reference 39. The extra stabilisation due to ligand-ligand interactions in these complexes depends on the character of the amino-acid side chains and amounts to 0.34 - 0.57 kJ/mole for combinations of aromatic and aliphatic side chains and 0.11 - 6.3 kJ/mole when arene - arene interactions are possible³⁹.

Sigel and co-workers⁴⁰ investigated the interaction between the aromatic rings of phenyl carboxylates (Ph-(CH₂)_n-CO₂) and 1,10-phenanthroline in ternary copper(II) complexes. Variation of the number of methylene units between the aromatic ring and the carboxylate group (n=0-5) revealed that the arene - arene interaction is most pronounced for n=1. This interaction is more efficient in a 60% 1,4-

dioxane-water mixture than in pure water⁴¹. Sigel et al.⁴² published a crystal structure of the complex with $n=2$, which revealed an edge-to-face orientation of the phenyl ring with respect to the 1,10-phenanthroline ring in a carboxylate bridged dinuclear complex. In the crystal, face-to-face stacking of the 1,10-phenanthroline ring with a neighbouring 1,10-phenanthroline ring was observed. Sigel et al.⁴³ have also performed extensive structural variation of the aryl group in $\text{Ar}-(\text{CH}_2)_n-\text{CO}_2^-$. Ternary complexes of these ligands with copper and zinc ions and 1,10-phenanthroline, again, revealed that the most efficient arene - arene interactions occur for the carboxylate ligands containing one methylene group. Of the large set of different aryl carboxylates that has been investigated, the compounds with a naphthyl or indole ring turned out to produce the most stable ternary complexes. Yamauchi and coworkers investigated the ternary complexes containing aromatic amines and aromatic β -amino acids. Structural variation of the amine as well as of the amino acid has been carried through⁴³. The efficiency of the ligand - ligand interaction increased in the series phenylalanine < tyrosine < tryptophan < 5-hydroxytryptophan. Also an increase in the size of the β -system of the aromatic amine ligand enhanced the arene - arene interaction. In the extreme case of the 5-hydroxy-L-tryptophan - Cu^{2+} - 1,10-phenanthroline complex a stability increase of 12.7 kJ/mole was observed.

Interestingly, the magnitude of the ligand - ligand interaction in the 5-hydroxy-L-tryptophan - Cu^{2+} - 2-(aminomethyl)pyridine complex, can be compared with the corresponding complex of dienophile **3.8**. For the former complex, Yamauchi⁴³ obtained an interaction Gibbs energy of 4.7 kJ/mole, whereas from the data in Table 3.2, a value of 5.6 kJ/mol can be calculated. The modest difference between these two values might well result from the more extended β -system in **3.8** as compared to that of 2-(aminomethyl)pyridine.

Unfortunately, these ternary copper complexes are difficult to study using NMR techniques, due to the paramagnetic character of the copper(II) ion. However, the corresponding square planar Pd(II) complexes exhibit comparable ligand - ligand interactions and results of NMR investigations of these complexes have been published. Yamauchi et al.⁴⁴ observed that, for complexes where arene - arene interactions are possible, the specific rotamer of the amino acid $\text{C}_\beta-\text{C}_\gamma$ bond corresponding to a face-to-face orientation of the aromatic amine ligand and the aromatic ring of the amino acid is favoured. Further evidence for a specific arene - arene interaction comes from the 0.7-1.2 ppm shifts of the ^1H -NMR signals of the amino acid ligand that are induced by the ring current of the diamine ligand⁴⁴.

From the temperature dependence of the stability constants of a number of ternary palladium complexes involving dipeptides and aromatic amines, the arene - arene interaction enthalpies and entropies have been determined⁴⁴. It turned out that the interaction is generally enthalpy-driven and counteracted by entropy. Yamauchi et al. hold a charge transfer interaction responsible for this effect. This suggestion is largely based upon the occurrence of a band at 300-350 nm in the UV spectrum⁴⁵.

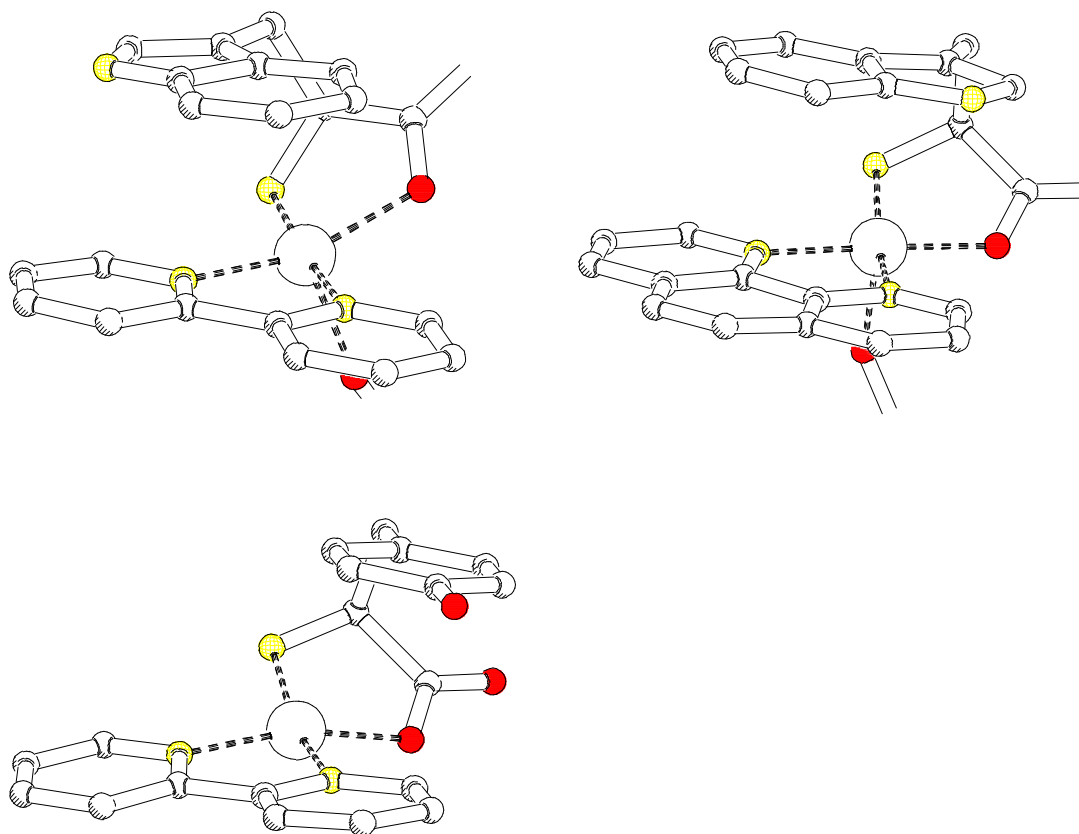


Figure 3.2. Crystal structures of (upper left) $\text{Cu}(\text{L-tryptophan})(2,2'\text{-bipyridine})\text{ClO}_4^{43}$; (upper right) $\text{Cu}(\text{L-Tryptophan})(1,10\text{-phenanthroline})\text{ClO}_4 \cdot 2.5\text{H}_2\text{O}^{46}$; and (lower) $\text{Cu}(\text{L-tyrosine})(2,2'\text{-bipyridine})\text{ClO}_4 \cdot 2.5\text{H}_2\text{O}^{45}$. The crystallographic data have been taken from the Cambridge Structural Database.

In their studies, Yamamauchi et al. also used dipeptides of aromatic amino acids and glycine or glutamic acid⁴⁴. Ternary palladium complexes with the latter ligands exhibit reduced ligand - ligand interactions as compared to the glycine dipeptide complexes due to steric interactions between the side chains of dipeptide⁴⁴. Using dipeptides containing two aromatic amino acid residues, structures have been suggested where the aromatic diamine is sandwiched between two aromatic rings⁴⁶.

Recent investigation of the effect of substituents in the para position of the phenylalanine ligand on the stability of the ternary complexes has revealed the sequence $\text{Br} > \text{OH} > \text{Cl} > \text{NH}_2 > \text{H} > \text{F}^{47}$. Interestingly, analysis of CD spectra indicates a reduction of the arene-arene interaction⁴⁵ upon addition of 1,4-dioxane to aqueous solutions of the mixed-ligand complexes, in disagreement with previous observations by Sigel⁴¹.

Crystal structures of complexes of copper(II) with aromatic amine ligands and α -amino acids^{45,47,48} and dipeptides⁴⁶ have been published. The structures of mixed ligand-copper complexes of L-tryptophan in combination with 1,10-phenanthroline and 2,2'-bipyridine and L-tyrosine in combination with 2,2'-bipyridine are shown in Figure 3.2. Note the subtle difference between the orientation of the indole ring in the two 1,10-phenanthroline complexes. The distance between the two

aromatic systems is comparable in both complexes: 3.67 Å in the 1,10-phenanthroline complex versus 3.51 Å in the 2,2'-bipyridine complex.

In summary, attractive ligand - ligand interactions in mixed ligand complexes are well documented. Compelling experimental evidence exists for this type of interaction in the solid state as well as in solution. Unfortunately, as yet no agreement exists on the nature of the interaction. However, some conclusions can be drawn which might prove to be helpful in future interpretations: (1) the arene - arene interactions are invariably enthalpy-driven and counteracted by a negative entropy change and (2) the substitution pattern on the aromatic ligands influences the interaction in a complicated fashion.

3.2.4 Effects of ligands on the endo-exo selectivity

The effect of ligands on the endo-exo selectivity of Lewis-acid catalysed Diels-Alder reactions has received little attention. Interestingly, Yamamoto et al.⁴⁹ reported an aluminium catalyst that produces mainly exo Diels-Alder adduct. The endo-approach of the diene, which is normally preferred, is blocked by a bulky group in the ligand.

In contrast, investigation of the effect of ligands on the endo-exo selectivity of the Diels-Alder reaction of **3.8c** with **3.9** demonstrated that this selectivity is not significantly influenced by the presence of ligands. The effects of ethylenediamine, 2,2'-bipyridine, 1,10-phenanthroline, glycine, L-tryptophan and L-abrine have been studied. The endo-exo ratio observed for the copper(II)-catalysed reaction in the presence of these ligands never deviated more than 2% from the endo-exo ratio of 93-7 obtained for catalysis by copper aquo ion.

3.2.5 Enantioselective catalysis

The attractive interaction between the aromatic ring of the dienophile and the aromatic group of the chiral α -amino acid ligands in ternary copper(II) complexes might well lead to shielding of one face of the dienophile to approach by the diene. This prompted an investigation of the effect of these ligands on the enantioselectivity of the copper(II)-catalysed Diels-Alder reaction of **3.8** with **3.9**. Indeed, it turned out that the Diels-Alder products can be obtained in quantitative yield in upto 74% enantiomeric excess (see Table 3.2)⁵⁰. Analogous studies of the nickel(II)-catalysed Diels-Alder reaction failed to induce significant enantioselectivity, which is not surprising in view of the large number of conceivable geometries of the ligand - nickel(II) - dienophile complex. Moreover, preliminary studies demonstrated that the arene - arene interaction is less pronounced for ternary nickel(II) complexes than for the corresponding copper(II) complexes⁵¹.

To the best of our knowledge the data in Table 3.2 constitute the first example of enantioselectivity in a chiral Lewis-acid catalysed organic transformation in aqueous solution. Note that for the majority of enantioselective Lewis-acid catalysed reactions, all traces of water have to be removed from the reaction mixture. Only in a limited number of reactions are small amounts of water tolerated^{29,52}. In

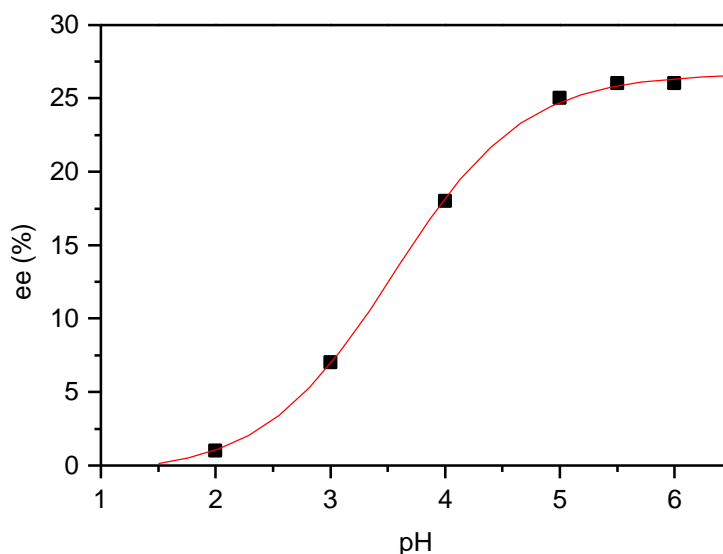


Figure 3.3. Enantiomeric excess of the Diels-Alder reaction of **3.8c** with **3.9** as a function of the pH.

exceptional cases one or a few equivalents of water have been reported to induce modest enhancements of the enantioselectivity⁵³.

The fact that enantioselective Lewis-acid catalysis of the Diels-Alder reaction between **3.8** and **3.9** in water is feasible has some pleasing consequences. It allows detailed investigation of the mechanism underlying enantioselectivity. In organic solvents these investigations are usually extremely complicated due to processes such as ion pairing and clustering of catalytically active species. These complications are generally not encountered in aqueous solution. The strong interactions between water and the reacting species that normally hamper catalysis by hard Lewis acids now turns into a significant benefit. For the first time a Lewis-acid catalysed reaction is available that allows easy and quantitative access to the relevant mechanistic parameters underlying enantioselective catalysis.

One example has already been encountered in the form of the binding constants in Table 3.2. These data form one of the first examples of compelling evidence for the involvement of attractive arene - arene interactions in determining the outcome of enantioselective catalysis. These attractive interactions have been frequently invoked as explanations for the observed enantioselectivities of Diels-Alder reactions^{25,54} and other transformations⁵⁵. Unfortunately, experimental evidence for these interactions is often only indirect^{54a,56}.

Despite the availability of relevant mechanistic parameters in the form of the rate constants and binding constants in Table 3.2, rationalisation of the observed enantioselectivities is still rather complicated and therefore some additional information has been gathered.

First, the pH-dependence of the enantioselectivity of the reaction between **3.8c** and **3.9** catalysed by the copper(L-tryptophan) complex has been studied. Above pH 5 the enantioselectivity reaches a plateau value (Figure 3.3). The diminished enantioselectivities observed at lower pH most likely

Table 3.3. Influence of temperature and ethanol content on the enantiomeric excess^a of the Diels-Alder reaction between **3.8c** and **3.9** catalysed by [Cu(L-tryptophan)]⁺ in aqueous solutions^b.

temperature (°C)	ethanol / water (v/v)							
	75 / 25		50 / 50		25 / 75		0 / 100	
	ee(%)	time (h)	ee(%)	time (h)	ee(%)	time (h)	ee(%)	time (h)
20	23	2	20	1	23	0.7	25	<0.7
0							28	1
-20					27	48		
-40	30	72						

^a Only the results of the major (>90%) endo isomer of the Diels-Alder adduct are shown.

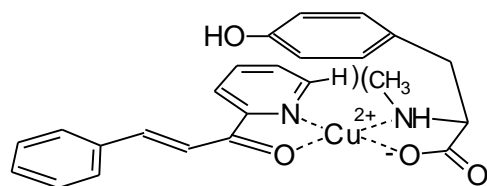
^b Conditions: [Cu(NO₃)₂] = 1.0 mM; [L-tryptophan] = 1.0 mM; [**3.8c**] = 10 mM; [**3.9**] = 24 mM.

result from protonation of the carboxylic acid group of the α -amino acid, which decreases the affinity of this ligand for the copper(II) ion and consequently favours catalysis by the achiral copper aquo ion. Furthermore, protonation of the pyridine ring of **3.8c** will result in Brønsted-acid catalysis of the reaction, leading to a racemic product mixture. Also the catalyst : dienophile ratio has been varied from 8 mM : 1 mM to 1 mM : 10 mM. Interestingly, this change did not significantly alter the enantioselectivity of the copper(L-tryptophan)-catalysed reaction, despite the fact that the former solution is homogeneous and the latter is heterogeneous. This is a strong indication that, as anticipated, the Diels-Alder reaction proceeds through the ternary dienophile - copper(II) - ligand complex and also that no displacement of the ligand by the dienophile takes place.

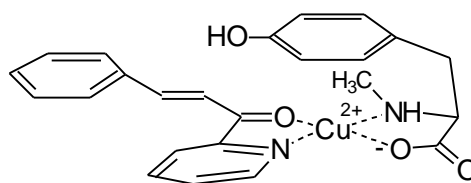
Likewise, the influence of the ligand : catalyst ratio has been investigated. Increase of this ratio up to 1.75 : 1 resulted in a slight improvement of the enantioselectivity of the copper(L-tryptophan)-catalysed Diels-Alder reaction. Interestingly, reducing the ligand : catalyst ratio from 1:1 to 0.5 : 1 resulted in a drop of the enantiomeric excess from 25 to 18 % instead of the expected 12.5 %. Hence, as anticipated, ligand accelerated catalysis is operative.

Finally the influence of the temperature and addition of ethanol on the enantioselectivity of the Diels-Alder reaction was studied. Table 3.3 summarises the results for different aqueous media. Apparently, changes in temperature as well as the presence of varying amounts of ethanol have only a modest influence on the selectivity of the Cu(tryptophan)-catalysed Diels-Alder reaction in aqueous solution. However, reaction times tend to increase significantly at lower temperatures. Also increasing the alcohol content induces an increase of the reaction times.

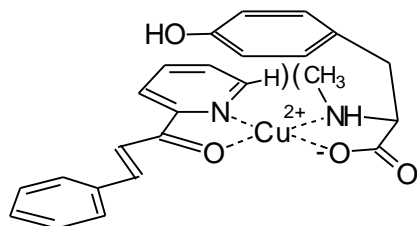
In summary, when using a ligand : catalyst ratio of 1.75 : 1 at pH 5-6 the enantioselectivity of the Diels-Alder reaction between **3.8c** and **3.9** is dictated by the activated complexes involving ligand, copper(II) ion, dienophile and diene. Considering that four different products are formed in this reaction (see Scheme 3.5), at least four different activated complexes are involved. However, each of these complexes has two degrees of freedom that determine the stereochemical outcome of the



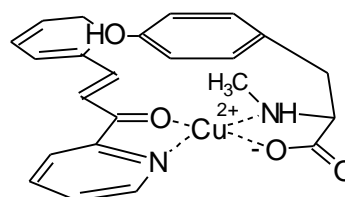
3.14a
cis - transoid \rightarrow (R,R)



3.14b
trans - transoid \rightarrow (S,S)



3.14c
cis - cisoid \rightarrow (S,S)



3.14d
trans - cisoid \rightarrow (R,R)

Scheme 3.10.

reaction: (1) the dienophile can coordinate in either the transoid or the cisoid conformation (**3.14a,b** or **3.14c,d** in Scheme 3.10, respectively) and (2) the coordination environment of the copper ion is characterised by either a cis or a trans geometry (**3.14a,c** or **3.14b,d**, respectively). Hence, the reaction can proceed through a total of 16 different activated complexes. When focusing on the major (>90%) endo isomer, still 8 different reaction pathways are conceivable, corresponding to (endo) approach of the diene on either the lower or upper face of complexes **3.14a-d**. It is highly probable that enantioselectivity arises from shielding of the upper side of these complexes by the aromatic ring of the γ -amino-acid ligand. Consequently, attack of the diene is likely to occur predominantly from the lower face. Hence, complexes **3.14a** and **d** can be expected to give predominantly (R,R)-endo-**3.10c**, whereas **3.14b** and **c** will yield the corresponding (S,S)-enantiomer.

For elucidating the course of the reaction, insight into factors that influence the position of the cisoid - transoid conformational, and cis - trans geometric equilibria is required. The literature on enantioselective Lewis-acid catalysed Diels-Alder reactions seems to point towards a general preference for the transoid conformation in the reaction of α,β -unsaturated esters^{20b,57}. In contrast, Evans proposed that the oxazaborolidine-catalysed Diels-Alder reaction depicted in Scheme 3.4 features the α,β -unsaturated N-acyloxazolidinone dienophile in the cisoid conformation²⁸. Interestingly, Corey et al.^{54a} suggested that the chiral titanium catalysed Diels-Alder reactions of a number of related oxazolidinones proceed through the transoid conformer⁵⁸. In conclusion, no reliable prediction can be made concerning the cisoid - transoid conformational equilibrium of **3.8** at this stage. Experiments using the copper(II)bisoaxazoline **3.6** as catalyst for the Diels-Alder reaction

between **3.8c** and **3.9** in anhydrous dichloromethane resulted in 16% ee of the same enantiomer as the one that is obtained in excess in the copper(II)(α -amino-acid) catalysed reaction in water. Assuming the catalyst dictates the conformation of the α,β -unsaturated ketone, this result suggests reaction of **3.8c** in water via the transoid conformation.

Fortunately, the experimental and literature data allow a more definite statement concerning the cis - trans geometric equilibrium. The large influence of a methyl substituent located on the α -amino-acid amine group on the enantioselectivity of the Diels-Alder reaction of **3.8c** with **3.9** forms the key to this problem. The cis complexes **3.14a** and **3.14c** most likely experience a steric repulsion between the pyridine β -hydrogen atom of the dienophile and the methyl group of the α -amino acid. This repulsion is absent in the trans complexes **3.14b** and **3.14d**. Hence, the methyl substituent in the α -amino acid ligand induces a preference for a trans geometry in the ternary complex.

This interpretation is supported by literature studies on copper(II) complexes containing two α -amino-acid ligands. For N-unsubstituted α -amino-acid ligands, deductions as to position of the cis - trans geometrical equilibrium in solution are difficult as illustrated by the fact that for some α -amino acids solid complexes have been isolated of both the cis and trans geometry³². In contrast it seems as if copper(II) complexes containing two N-alkylated α -amino-acid ligands crystallise exclusively in the trans form⁵⁹.

Interestingly, the N-methylated aromatic α -amino acids increase the affinity of the catalyst for the dienophile (see Table 3.2). One might envisage three effects that could be responsible for this behaviour. Possibly, in the ternary complex the N-methyl group forces the aromatic ring of the α -amino acid more towards the pyridine ring of the dienophile. Another explanation involves a steric interaction between the N-methyl group of the α -amino acid ligand and the water molecule that is coordinated in the apical position. This interaction facilitates the displacement of this water molecule which is required in order for the arene - arene interaction to occur. Finally, there are indications that the arene - arene interactions are most favourable for the trans complex (see Figure 3.2). If the methyl groups are able to force the dienophile into a complete trans coordination, this may well result in an enhanced stability of the ternary complex.

In conclusion, the Diels-Alder reaction of **3.8c** with **3.9** most likely proceeds largely through either complex **3.14b** or **3.14d**, which differ in the orientation of the reacting double bond with respect to the carbonyl group and, more importantly, differ in the absolute configuration of the major Diels-Alder adduct that is produced. If insight into this absolute configuration could be obtained, the reaction pathway leading to the major product could be identified. Unfortunately, despite extensive efforts, this problem has not yet been solved.

3.2.6 Solvent effect on the enantioselectivity⁶⁰

Having available, for the first time, a reaction that is catalysed by Lewis acids in water in an enantioselective fashion, the question rises how water influences the enantioselectivity. Consequently,

Table 3.4. Enantiomeric excess and reaction times of the copper(L-abrine)-catalysed Diels-Alder reaction of **3.8c** with **3.9** in different solvents at 0 °C.

solvent	time (days)	ee(%) ^c
water ^a	3	74
ethanol ^b	10	39
acetonitrile ^b	7	17
THF ^b	8	24
chloroform ^b	11	44

^a Conditions: [Cu(NO₃)₂] = 1.0 mM; [L-abrine] = 1.75 mM; [**3.8c**] = 10 mM; [**3.9**] = 24 mM. One equivalent of NaOH was used to deprotonate the amino acid. ^b Conditions: [Cu(OTf)₂] = 1.0 mM; [L-abrine] = 1.75 mM; [**3.8c**] = 10 mM; [**3.9**] = 80 mM. One equivalent of triethylamine was used to deprotonate the amino acid. ^c Only the results of the major (>90%) endo isomer of the Diels-Alder adduct are shown.

the copper(II) catalysed reaction between **3.8c** and **3.9** in the presence of L-tryptophan and L-abrine has been performed in a number of organic solvents. To reduce the influence of ion pairing^{28b}, we used the copper(II)triflate instead of copper(II)nitrate in the organic solvents. For deprotonation of the α -amino-acid ligand, triethylamine was used instead of sodium hydroxide, which is employed in aqueous media. Table 3.4 summarises the results.

Note that the reaction time in water is considerably shorter than that in organic solvents, despite the fact that the concentration of diene used for the reaction in water was less than one third of that for the reaction in the organic solvents. Contrary to the organic solvents, the reaction mixture in water is heterogeneous. It might well be that the low solubility of the Diels-Alder product (**3.10c**) in this solution reduces inhibition of the reaction by this compound. Consequently, product inhibition is likely to be more pronounced in the organic media.

Due to the prolonged reaction times in organic solvents, dimerisation of the diene occurs during the reaction, resulting in contaminated product mixtures after work-up. In contrast the reactions in water yield quantitatively the ¹H-NMR-pure Diels-Alder adducts.

Most importantly, enantioselectivity benefits considerably from the use of water. This effect could be a result of water exerting a favourable influence on the cisoid - transoid equilibrium. Unfortunately, little is known of the factors that affect this equilibrium. Alternatively, and more likely, water enhances the efficiency of the arene - arene interactions. There is support for this observation^{34,61}.

Since arene-arene interactions are held responsible for the enantioselectivity in many reactions involving chiral catalysts, we suggest that the enhancement of enantioselectivity by water might well be a general phenomenon.

Assuming London-dispersion and electrostatic interactions to be dominant in arene - arene interactions (see Section 3.2.7), the solvent effect on the enantioselectivity is anticipated to be influenced by the polarisability and polarity of the solvent. The arene -arene interaction is inferred to

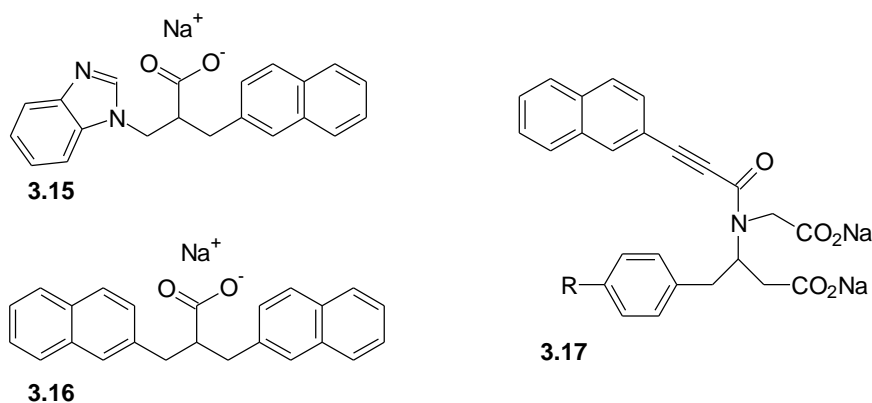
be most efficient in solvents that are characterised by weak London-dispersion interactions (low polarisability). Note that water has an exceptionally low polarisability ($\alpha = 1.44$ versus 4.41 - 8.53 for the other solvents in Table 3.4)⁶². Unfortunately, no satisfactory correlation between solvent polarisability and the solvent effect on enantioselectivity is observed. Particularly the relatively high enantioselectivity of the Diels-Alder reaction in chloroform ($\alpha = 8.53$) is in discord with an important role of the polarisability in diminishing arene - arene interactions. However, since the arene - arene interaction is accompanied by displacement of a solvent molecule from the apical position of the copper ion, it might well be that poorly coordinating solvents, such as chloroform, have an intrinsic advantage over coordinating solvents. Likewise solvent polarity can be expected to affect the electrostatic component of the arene - arene interaction, but again, no satisfactory correlation between enantioselectivity and the $E_T(30)$ solvent polarity parameter was observed. Unfortunately a two-parameter analysis using both solvent polarisability and solvent polarity also failed.

Clearly, complete understanding of solvent effects on the enantioselectivity of Lewis-acid catalysed Diels-Alder reactions has to await future studies. For a more detailed mechanistic understanding of the origins of enantioselectivity, extension of the set of solvents as well as quantitative assessment of the strength of arene - arene interactions in these solvent will be of great help.

3.2.7 Investigations into the nature of the arene - arene interaction

Arene - arene interactions are emerging as important contributors to not only the enantioselectivity of organic reactions⁶³, but also to molecular recognition⁶⁴ and protein folding⁶⁵. Likewise arene - arene interactions are involved in determining the structure of nucleic acids⁶⁶. The nature of these interactions is still a matter of considerable controversy. Or, as Hunter⁶⁷ puts it: "When molecular scientists obtain an unexpected result in a system which contains π -systems, they tend to invoke the mythical powers of the π - π interaction, π -stacking, charge transfer, π -acid/ π -base or electron donor - acceptor interaction.". Even the geometry in which the arene groups interact most efficiently is still under debate. For the benzene dimer, computer simulations and experimental results indicate that an edge-to-face orientation is favoured over the face-to-face, or stacked geometry⁶⁸. On the basis of Monte-Carlo simulations, Jorgensen et al.⁶⁸ conclude the same preference for the edge-to-face arrangement for the benzene dimer in water. Comparison of the results obtained for water with calculations for chloroform and benzene as solvents demonstrated that the formation of a dimer is more favourable in aqueous solution than in the organic solvents. Interestingly, upon increasing the size of the aromatic ring system, the stacked structures become increasingly favourable⁶⁸. In contrast, recent gas-phase calculations by Jaffe and Smith⁶⁹ identified the face to face geometry of the benzene dimer as the most favourable.

A number of different types of interactions have been suggested as contributing to the arene -arene interactions. London dispersion forces are likely to be of influence^{69,70}. Also hydrophobic interactions may be important⁷¹. Finally, electrostatic interactions as well as donor acceptor interactions have



Scheme 3.11.

been invoked^{67,72}. The distinction between the latter is largely based upon the influence of substituents: donor - acceptor interactions are favoured by electron withdrawing substituents on one ring and electron donating substituents on the other, whereas purely electrostatic interactions are favoured by the presence of electron withdrawing substituents on both rings that reduce the repulsion between the π -electron clouds in a face-to-face arrangement.

In an elegant study, Gellman et al.⁷³ analysed the conformation of diaryl compounds **3.15** and **3.16** (Scheme 3.11). NMR investigations revealed that **3.15** exhibits considerable stacking propensity, whereas no evidence for a naphthyl - naphthyl association could be detected for **3.16**. The absence of stacking in **3.16** was interpreted as evidence against the importance of hydrophobic interactions. Gellman et al.⁷³ ascribed the arene - arene interaction in **3.15** to electrostatic interactions between partial charges in the aromatic rings. Surprisingly, in a recent study of the conformation of **3.17**, Gellman et al.⁷⁴ assumed that the observed stacking in this compound is completely driven by hydrophobic interactions, despite poor correlation between Gibbs energies of hydration of the R substituent and the tendency for stacking.

The literature on arene - arene interactions in ternary metal-ion complexes, as reviewed in Section 3.2.3, indicates that these interactions are generally enthalpy-driven and counteracted by a reduction of the entropy^{34,37a,41,44}. We have determined the changes in enthalpy and entropy for the process of binding of **3.8c** to a number of copper(II)-amino acid complexes from temperature dependent measurements of the equilibrium constants. The results are summarised in Table 3.5.

Table 3.5. ΔG° , ΔH° and ΔS° for the binding of **3.8c** to different copper(II)-amino acid complexes in water at 25 °C at pH 5-6.

Δ -amino acid	ΔG° (kJ/mole)	ΔH° (kJ/mole)	$T\Delta S^\circ$ (kJ/mole)
-	-17.7	-18.7	-1.0
glycine	-16.0	-14.1	1.9
L-tryptophan	-19.9	-25.0	-5.1
L-abrine	-21.1	-34.0	-12.9

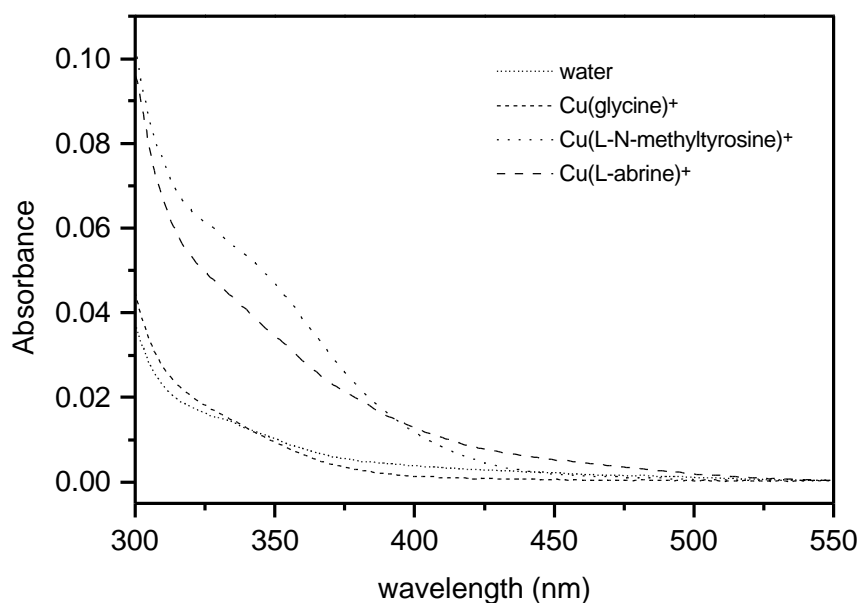


Figure 3.4. UV-vis absorption spectra of **3.10c** in water and in water containing 3.0 mM of Cu(glycine) complex, 3.0 mM of Cu(N-methyl-L-tyrosine) and 3.0 mM of Cu(L-abrine).

Clearly, the same picture emerges of enthalpy-driven and entropy-counteracted arene - arene interactions. These data are hard to reconcile with a hydrophobic driving force, since at room temperature, in the absence of cosolutes, hydrophobic interactions are normally driven by the gain in entropy upon release of water molecules from hydrophobic hydration shells (see Section 1.3). Note, however, that examples are known of enthalpy-driven hydrophobic interactions⁷⁵. These processes involve binding of a nonpolar solute in a nonpolar cavity. In that case an enthalpy gain upon binding is expected, since filling the cavity with water molecules is inevitably accompanied by a sacrifice of hydrogen bonds (endothermic). Hence, expelling the water molecules from the cavity into bulk solution will be exothermic.

In contrast, the hydration of the aromatic side chains of α -amino acids is characterised by a reduction of entropy, and, judging from the modest enthalpy change upon transfer from the gas phase to water, no significant breaking of hydrogen bonds takes place⁷⁶. Likewise, the hydration of a pyridine rings is generally characterised by a significant decrease in entropy^{76b,c}. At the onset of an arene - arene interaction, partial dehydration of the aromatic groups has to take place, which will inevitably be characterised by a gain in entropy. Hence, a hydrophobic contribution in the arene - arene interaction is anticipated to reveal its presence in the entropy term. Apparently, this entropy gain is overwhelmed by another effect. Hence, the hydrophobic interaction is not the major driving force for the arene - arene interactions, although it is anticipated to contribute to some extent.

An alternative driving force could involve a donor - acceptor interaction. The electron-poor pyridine ring that is coordinated to the copper cation can act as electron acceptor with respect to the aromatic ring of the α -amino acid. The fact that donating substituents on the amino acid increase the efficiency

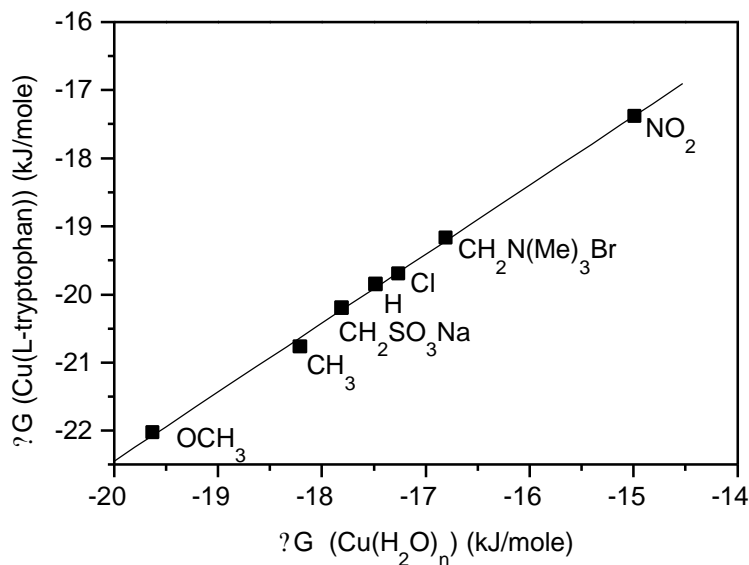


Figure 3.5. Gibbs energies of complexation of **3.8a-g** to the copper(II)(L-tryptophan) complex versus those for complexation to copper aquo ion.

of the arene - arene interaction (Table 3.2) seems to support this view. Furthermore, a charge transfer band is observed between 300 and 400 nm for the complexes that exhibit efficient arene - arene interactions (Figure 3.4)⁷⁷. This observation demonstrates that the orbitals of the dienophile and the π -amino acid ligand are sufficiently close for overlap. As correctly pointed out by Cozzi et al.⁷⁸, the occurrence of a charge transfer band in itself cannot be considered as evidence for a donor - acceptor interaction. This band owes its existence to the possibility of forming a charge-separated excited state, which normally contributes little to ground-state stability.

When a donor - acceptor interaction is operative, one would expect that electronic effects of substituents on the dienophile will affect this interaction. Consequently, one might anticipate an increase of the substituent effect on the equilibrium constant for binding of the dienophile to the copper(ligand) complex for aromatic amino acids beyond the value that is obtained for binding to the copper aquo ion. Surprisingly, no indication for such behaviour is observed. A plot of the Gibbs energies of complexation of **3.8a-g** to the copper(II)(L-tryptophan) complex versus those for binding to the copper aquo ion is shown in Figure 3.5. A straight line is obtained with a slope of 1.01 ($r=0.999$). Evidently, the Hammett ρ -values describing the substituent effect on binding of the dienophile to the copper(L-tryptophan) complex (-0.52) is, within experimental error, equal to that for binding to the copper aquo ion (-0.51). This correlation demonstrates that substituents on the phenyl ring of the dienophile do not have a significant influence on the magnitude of the arene - arene interaction. Also the enantioselectivity of the reaction of **3.8b**⁷⁹ and **3.8g** with **3.9** catalysed by copper(L-abrine) in water is, within experimental error, equal to the enantioselectivity observed for **3.8c**.

From the absence of a significant substituent effect on the complexation as well as the

enantioselectivity, we conclude that the arene - arene interaction is not driven by a donor - acceptor interactions.

In summary, there are indications that neither hydrophobic interactions, nor donor- acceptor interactions are predominantly driving the arene - arene interaction. Consequently, we contend that these interactions are mainly governed by London - dispersion and electrostatic forces.

The beneficial effect of water in the arene - arene interaction can be explained by the fact that this solvent is characterised by a low polarisability so that interactions of the aromatic rings with water are less efficient than with most organic solvents. Also the high polarity of water might lead to a polarisation of the aromatic rings, thereby enhancing electrostatic interactions. Finally, hydrophobic interactions may be expected to play a modest role.

3.3 Conclusions and outlook

In the absence of specific interactions, ligands tend to reduce the efficiency of copper(II) and nickel(II) catalysis of the Diels-Alder reaction between **3.8c** and **3.9**. This trend is a consequence of diminished equilibrium constants for binding of the dienophile to the catalyst as well as decreased rate constants for the reaction of the resulting complex with the diene in the presence of the ligand. In special cases, specific interactions can cause a deviation from this behaviour. Most interestingly, the binding of the dienophile to copper complexes of aromatic α -amino acids benefits considerably (up to 5.6 kJ/mole) from an enthalpy-driven arene - arene interaction between the aromatic ring of the α -amino acid and the pyridine ring of the dienophile, leading to ligand - accelerated catalysis. There are indications that the arene - arene interaction is governed mainly by London-dispersion and electrostatic forces. These interactions dictate the conformation of the ternary dienophile - copper(II) - ligand complex leading to shielding of one face of the dienophile for approach by the diene. Consequently, enantioselectivity (up to 74% ee) is induced in the Diels-Alder reaction of the ternary dienophile - copper(II) - aromatic α -amino acid complexes with diene **3.9**. Interestingly, enantioselectivity benefits markedly from the use of water as the solvent. Use of this solvent also leads to cleaner reactions and reduced reaction times.

The fact that, for the first time, enantioselectivity is observed in an organic reaction catalysed by a chiral Lewis-acid in water opens new possibilities. Since the arene-arene interactions that are underlying enantioselectivity of the particular Diels-Alder reaction described in this chapter are also held responsible for the enantioselectivity in many other reactions involving chiral catalysts, we infer that the enhancement of enantioselectivity by water might well be a general phenomenon. Hence, future water-promoted enantioselectivity of other organic transformations is envisaged. Moreover, the use of water facilitates mechanistic studies of catalysed reactions and can be expected to contribute to a deeper understanding of the interactions underlying enantioselective catalysis. The extensive knowledge and large set of techniques of coordination chemistry in water can now be successfully employed in enantioselective catalysis.

3.4 Experimental section

Materials

Cu(NO₃)₂·3H₂O (Merck), Cu(OTf)₂ (Aldrich), Ni(NO₃)₂·6H₂O (Merck), KNO₃ (Merck), 2,2'-bipyridine (Merck), 1,10-phenanthroline (Merck) and N,N'-dimethylethylenediamine (Aldrich) were of the highest purity available. Ethylenediamine (Aldrich) and 2-(aminomethyl)pyridine (Aldrich) were distilled prior to use. Glycine (Fluka), L-valine (Fluka), L-leucine (Aldrich), L-phenylalanine (Jansen), L-tyrosine (Aldrich), N-methyl-L-tyrosine (Bachem), N-methyl-p-methoxy-L-phenylalanine (Bachem), L-tryptophan (Acros), 5-hydroxy-L-tryptophan (Sigma) and N-methyl-L-tryptophan (L-abrine, Aldrich) were of the highest purity available. N,N-dimethyl-L-tyrosine was synthesised as described by Bowman⁸⁰. Dimineralised water was distilled twice in a quartz distillation unit. Ethanol (Merck), chloroform (Merck) and THF (Merck) were of the highest purity available. Acetonitrile (Janssen) was run over basic aluminium oxide prior to use. Cyclopentadiene (**3.9**) was prepared from its dimer (Merck-Schuchardt) immediately before use. The preparation of dienophiles **3.8a-g** has been described in Chapter 2. Europium tris-(3-(trifluormethylhydroxymethylene)-d-camphorate) was obtained from Aldrich.

Equilibrium constants and enthalpies and entropies of complexation

Equilibrium constants for binding of **3.8a-g** were determined following methods described in Chapter 2. Solutions containing copper(II) or nickel(II) α -amino acid complexes were prepared by adding a clear solution (heating may be required) of the ligand in 1-5 ml of water containing 1 equivalent of sodium hydroxide to a solution of the transition metal salt in 1-5 ml water in a volumetric flask. The required amount of potassium nitrate was added together with an amount of water sufficient to fill 95% of the volume. After dissolution of the potassium nitrate and thermal equilibration, the pH was adjusted to the desired value using diluted nitric acid and filling of the volumetric flask with water was completed.

The enthalpies of complexation of **3.8c** to the copper(II) - amino acid ligand complexes have been calculated from the values of K_a at 20 °C, 25 °C, 30 °C, 40 °C and 50 °C using the van't Hoff equation⁸¹. Complexation entropies have been calculated from the corresponding Gibbs energies and enthalpies.

Kinetic measurements

Kinetic experiments were performed on a Perkin Elmer λ 2, λ 5, or λ 12 spectrophotometer following methods described in Chapter 2. Values for k_{cat} , given in Tables 3.1 and 3.2 were calculated using equation A8, derived in Appendix 2.1 in Chapter 2.

Endo-exo selectivity

In a typical experiment 105 mg (0.50 mmol) of **3.8c**, dissolved in a minimal amount of ethanol, and 100 mg (1.50 mmol) of **3.9** were added to a solution of 1.21g (5 mmol) of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ and 5 mmol of ligand in 500 ml of water in a 500 ml flask. α -Amino-acid containing solutions required addition of one equivalent of sodium hydroxide. When necessary, the pH was adjusted to a value of 5 (α -amino acids) and 7.5 (amines). The flask was sealed carefully and the solution was stirred for 2-4 hours, followed by extraction with ether. After drying over sodium sulfate the ether was evaporated. The endo-exo ratios were determined from the $^1\text{H-NMR}$ spectra of the product mixtures as described in Chapter 2.

Enantioselective catalysis

In a typical procedure, a solution of 0.175 mmol of L- α -amino acid and 0.175 mmol of NaOH in 1 ml of water was added to a solution of 0.100 mmol of $\text{Cu}(\text{NO}_3)_2$ in 100 ml of water in a 100 ml flask. The pH was adjusted to 6.0-6.5. The catalyst solution was cooled to 0°C and a solution of 1.0 mmol of **3.8c** in a minimal amount of ethanol was added, together with 2.4 mmol of **3.9**. The flask was sealed carefully. After 48 hours of stirring at 0°C the reaction mixture was extracted with ether, affording **3.10c** in quantitative yield. After evaporation of the ether from the water layer (rotary evaporator) the catalyst solution can be reused without a significant decrease in enantioselectivity.

Determination of the enantiomeric excess

The enantiomeric excess of **3.10c** has been determined by HPLC analysis using a Daicel Chiracel OD column and eluting with a 60 / 1 (v/v) hexane(HPLC-grade) / 2-propanol(p.a.) mixture. At a flow of 1 ml per minute the retention times for the different isomers of **3.10c** were: 6.3 min. (exo, major enantiomer); 7.1 min. (exo, minor enantiomer); 7.7 min. (endo, major enantiomer); 10.7 min. (endo, minor enantiomer).

The enantiomeric excess of **3.10b** and **3.10g**, has been determined from $^1\text{H-NMR}$ measurements (Varian VXR 300 MHz) in the presence of the chiral europium tris-(3-(trifluoromethylhydroxymethylene)-d-camphorate) ($\text{Eu}(\text{tfc})_3$) shift reagent. To a solution of 100 mg of Diels-Alder adduct in 0.7 ml of CDCl_3 , 10-25 μl portions of a solution of 30 mg of $\text{Eu}(\text{tfc})_3$ in 250 μl of CDCl_3 were added and the $^1\text{H-NMR}$ spectrum was recorded. For the enantiomers of endo-**3.10g**, the signals of one of the vinyl protons ($\delta = 5.82$ ppm in the absence of shift reagent) were baseline separated after addition of 65 μl (0.2 eq.) of the solution of the shift reagent. For **3.10b** the singlet of the phenyl protons at 7.15 ppm (in the absence of shift reagent) was monitored. After addition of 125 μl (0.5 eq.) of the solution of the shift reagent, the enantiomeric excess was determined after integration of the signal of the minor enantiomer (7.06 ppm, s, 4H) and of half of the significantly shifted and splitted signal of the major enantiomer (7.25 ppm, d, 2H).

Determination of the enantiomeric excess of **3.10c** has also been performed using $\text{Eu}(\text{tfc})_3$. Results

obtained using this methods agreed within 2% with the outcome of the HPLC analysis.

Acknowledgements

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- 79 Interestingly, after one crystallisation from *iso*-octane the major enantiomer of **3.8b** can be obtained in higher than 99% ee by evaporation of the mother liquor. Unfortunately, the oily product mixture still contained both enantiomers of the *exo* isomer, which could not be separated by chromatography.
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The Scope of Lewis-Acid Catalysis of Diels-Alder Reactions in Water

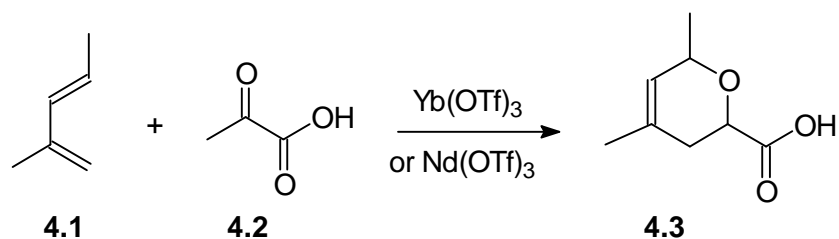
The merits of (enantioselective) Lewis-acid catalysis of Diels-Alder reactions in aqueous solution have been highlighted in Chapters 2 and 3. Both chapters focused on the Diels-Alder reaction of substituted 3-phenyl-1-(2-pyridyl)-2-propene-1-one dienophiles. In this chapter the scope of Lewis-acid catalysis of Diels-Alder reactions in water is investigated. Some literature claims in this area are critically examined and requirements for effective Lewis-acid catalysis are formulated. Finally an attempt is made to extend the scope of Lewis-acid catalysis in water by making use of a strongly coordinating auxiliary.

4.1 Introduction

At the outset of the work described in this thesis, a number of questions were formulated. Given the substantial benefits of water with respect to the uncatalysed Diels-Alder reaction, the most important question addressed the possibilities of transferring these benefits to the Lewis-acid catalysed reaction. It soon became obvious that this could not easily be achieved, since the majority of Diels-Alder reactants have a negligible tendency to interact with a Lewis-acid catalyst in water. Fortunately, the affinity of a Diels-Alder reactant for Lewis-acids can increase dramatically if the possibility of forming a chelate exists. In Chapter 2 it was demonstrated that, by following this approach, Lewis-acid catalysis of a Diels-Alder reaction in water is feasible. Moreover, it turned out that part of the beneficial effect of water on the uncatalysed Diels-Alder reaction is retained in the Lewis-acid catalysed counterpart. The studies in Chapter 2, and also in Chapter 3, employed a dienophile that has been specifically designed for bidentate binding to the Lewis-acid catalyst. To accomplish this a pyridine ring was fused to a α,β -unsaturated ketone fragment allowing coordination through formation of a 5-membered ring chelate. The encouraging results obtained for the Diels-Alder reaction of this molecule prompted investigation of the possibilities of extending these results to other Diels-Alder reactions. Attempts in this direction are described in this chapter, but first the literature claims of Lewis-acid catalysis of Diels-Alder reactions in water are critically examined.

4.1.1 Literature claims of Lewis-acid catalysis of Diels-Alder reactions in water

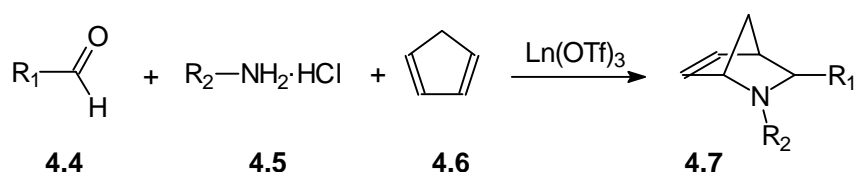
At the time of the printing of this thesis eight reports describe Lewis-acid catalysis of Diels-Alder reactions in water. This small number indicates that Lewis-acid catalysis in aqueous media suffers not only from unpopularity, but also from an intrinsic disadvantage. Three of these reports originate



Scheme 4.1.

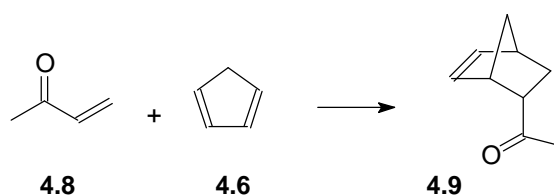
from the work described in Chapter 2 and 3¹, wherein the dienophile is capable of forming a chelate with the Lewis-acid. Likewise, Lubineau² described the effect of lanthanide triflates on the hetero Diels-Alder reaction of glyoxylate with 2-methyl-1,3-pentadiene (Scheme 4.1). Also here, glyoxylate acts as a dienophile capable of binding in a bidentate fashion to the Lewis-acid catalyst.

Another hetero Diels-Alder reaction has been described by Wang et al.³. In this process the azadienophile is formed in situ from an aldehyde and an amine under acidic conditions (Scheme 4.2). The labile dienophile is trapped by reaction with the diene. The groups of Grieco⁴ and Waldmann⁵ have demonstrated that this type of reaction proceeds readily in aqueous media. Wang et al.³ observed an increase in the yield of this Diels-Alder reaction upon introduction of lanthanide triflates³. Unfortunately, it is not clear whether the presence of the lanthanide ions directly influences the rate of the Diels-Alder reaction or whether the observed improvement of the yield results primarily from a beneficial influence on the pre-equilibrium in which the dienophile is formed. Moreover, judging from the concentrations of the reactants, the reaction mixtures are heterogeneous, which complicates analysis, due to the possibility of transport limitations and of local concentration differing from overall concentrations.



Scheme 4.2.

In recent reports by Loh et al.⁶ and by Zhu and Espenson⁷, Diels-Alder reactions have been performed in heterogeneous aqueous mixtures in the presence of a Lewis-acid catalyst. Loh et al.⁶ have studied the effect of indium trichloride on a series of common Diels-Alder reactions, most of



Scheme 4.3.

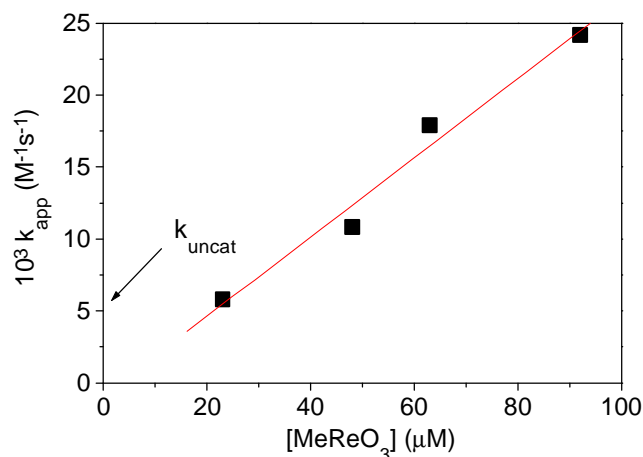


Figure 4.1. The apparent rate constant of the Diels-Alder reaction of **4.8** with **4.6** versus the concentration of MeReO₃ catalyst according to reference 7.

which feature *monodentate* reactants. The work of Loh has been criticised by Kobayashi⁸. Also Zhu and Espenson⁷ report a beneficial effect of methylrhenium trioxide on a number of Diels-Alder reactions involving *monodentate* reactants. Zhu and Espenson report a kinetic study of the effect of the catalyst on the reaction of methyl vinyl ketone with cyclopentadiene (Scheme 4.3). Addition of methylrhenium trioxide is reported to lead to a 4-fold acceleration. The dependence of the observed rate constant on the concentration of methylrhenium trioxide is reported to be linear (Figure 4.1). Note that extrapolation of the rate constant to zero catalyst concentration produces an intercept close to zero, which is at least an order of magnitude lower than the rate constant for the uncatalysed reaction. This is puzzling, since usually the overall rate constant of a catalysed reaction results from simple addition of the rate constant of the uncatalysed reaction and the rate constant of the catalysed reaction. Hence, upon extrapolation of the rate constant to zero catalyst concentration, the intercept is expected to equal the rate constant of the uncatalysed reaction. However, this pattern is not observed by Zhu and Espenson⁷, who do not provide an explanation for this peculiar behaviour.

In summary, the groups of Espenson⁷ and Loh⁶ observe catalysis of Diels-Alder reactions involving monodentate reactants by Lewis acids in water. If their observations reflect Lewis-acid catalysis, involving coordination and concomitant activation of the dienophile, we would conclude that Lewis-acid catalysis in water need not suffer from a limitation to chelating reactants. This conclusion contradicts our observations which have invariably stressed the importance of a chelating potential of the dienophile. Hence it was decided to investigate the effect of indium trichloride and methylrhenium trioxide under homogeneous conditions.

The results of a study of the effect of these catalysts on the model Diels-Alder reaction of methyl vinyl ketone (**4.8**) with cyclopentadiene (**4.6**) are summarised in Table 4.1

Clearly, under homogeneous conditions, no significant catalytic effect is observed. Note that we have not been able to reproduce the kinetic data reported by Espenson et al.⁷. We conclude that the

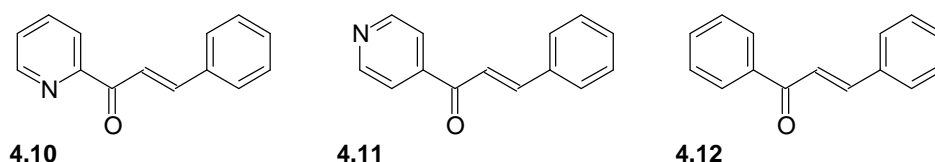
Table 4.1. Second-order rate constants for the Diels-Alder reaction of **4.8** with **4.6** in water and in water containing MeReO₃ or InCl₃ at 25 °C.

catalyst	catalyst concentration (mM)	k_{app} (M ⁻¹ s ⁻¹)
-	-	$5.18 \cdot 10^{-2}$
MeReO ₃	0.1	$5.25 \cdot 10^{-2}$
InCl ₃	13	$4.91 \cdot 10^{-2}$

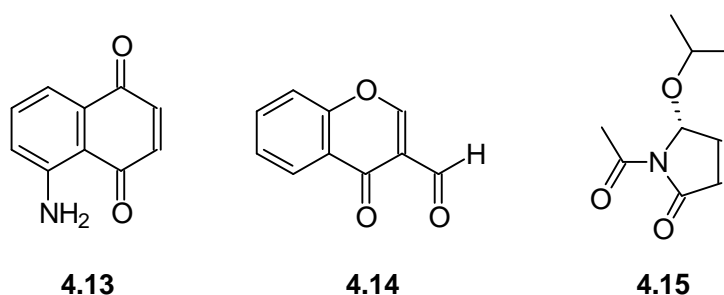
increase in the yield of the Diels-Alder reactions as reported by Loh and also by Espenson does *not* result from direct activation of the dienophile by the Lewis-acid catalyst. This confirms our notion that a chelating character of the reactants is a prerequisite for efficient Lewis-acids catalysis in water.

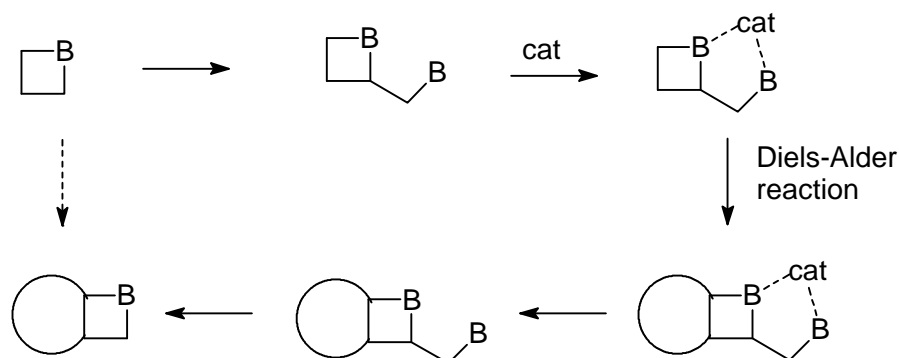
4.2 Results and discussion

On the basis of the studies described in the preceding chapters, we anticipated that chelation is a requirement for efficient Lewis-acid catalysis. This notion was confirmed by an investigation of the coordination behaviour of dienophiles **4.11** and **4.12** (Scheme 4.4). In contrast to **4.10**, these compounds failed to reveal a significant shift in the UV absorption band maxima in the presence of concentrations up to one molar of copper(II)nitrate in water. Also the rate of the reaction of these dienophiles with cyclopentadiene was not significantly increased upon addition of copper(II)nitrate or ytterbium(III)triflate.

**Scheme 4.4.**

Consequently, in initial attempts to extend the scope, we aimed to identify catalysis of Diels-Alder reactions of other *bidentate* dienophiles in water. This task turned out to be more difficult than expected. Scheme 4.5 provides a collection of potentially chelating dienophiles that all failed to

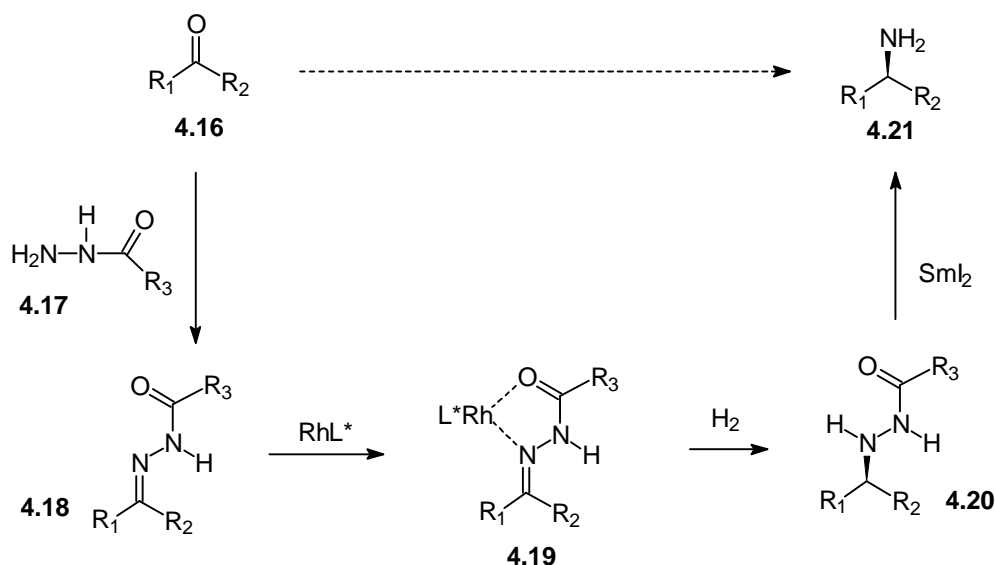
**Scheme 4.5.**



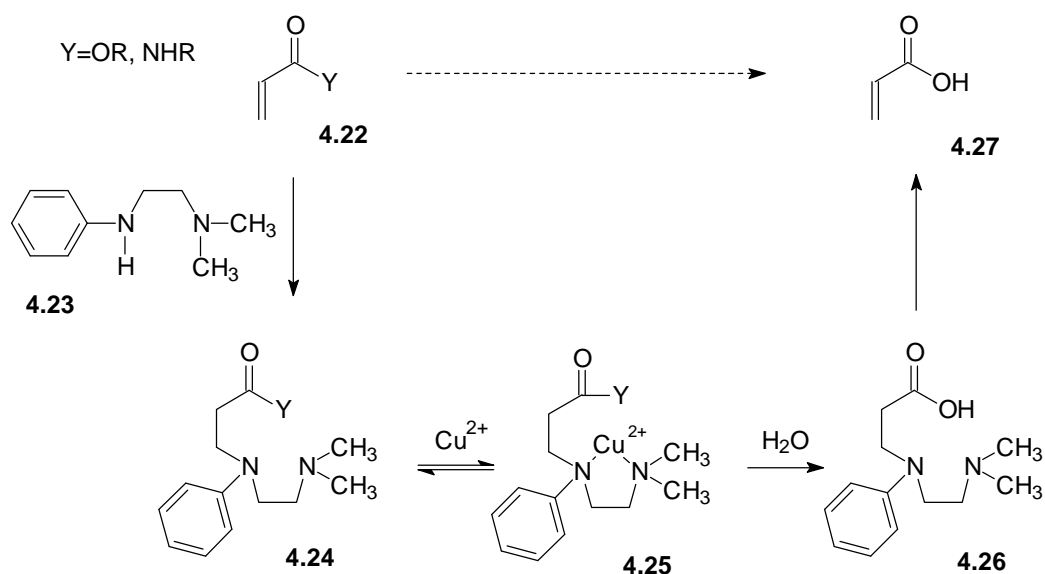
Scheme 4.6. Schematic representation of the use of a coordinating auxiliary for Lewis-acid catalysis of a Diels-Alder reaction.

exhibit Lewis-acid catalysed Diels-Alder reactions. Previous studies by Wijnen⁹ demonstrated that dienophile **4.13** has little affinity for the Lewis acids tested so far. Likewise, **4.14** and **4.15**, which have the potential of forming six-membered ring chelates with metal ions, refrain from doing so in water (Scheme 4.5). Apparently, chelation in aqueous solution is rather demanding and a search for extending the scope of the reaction in this direction is not particularly promising. Moreover, ideally, one would want common *monodentate* dienophiles to undergo Lewis-acid catalysed Diels-Alder reactions in aqueous solution.

This goal might well be achieved by introducing an auxiliary that aids the coordination to the catalyst. After completion of the Diels-Alder reaction and removal of the auxiliary the desired adduct is obtained. This approach is summarised in Scheme 4.6. Some examples in which a temporary additional coordination site has been introduced to aid a catalytic reaction have been reported in the literature and are described in Section 4.2.1. Section 4.2.2 relates an attempt to use (2-pyridyl)hydrazone as coordinating auxiliary for the Lewis-acid catalysed Diels-Alder reaction,



Scheme 4.7.



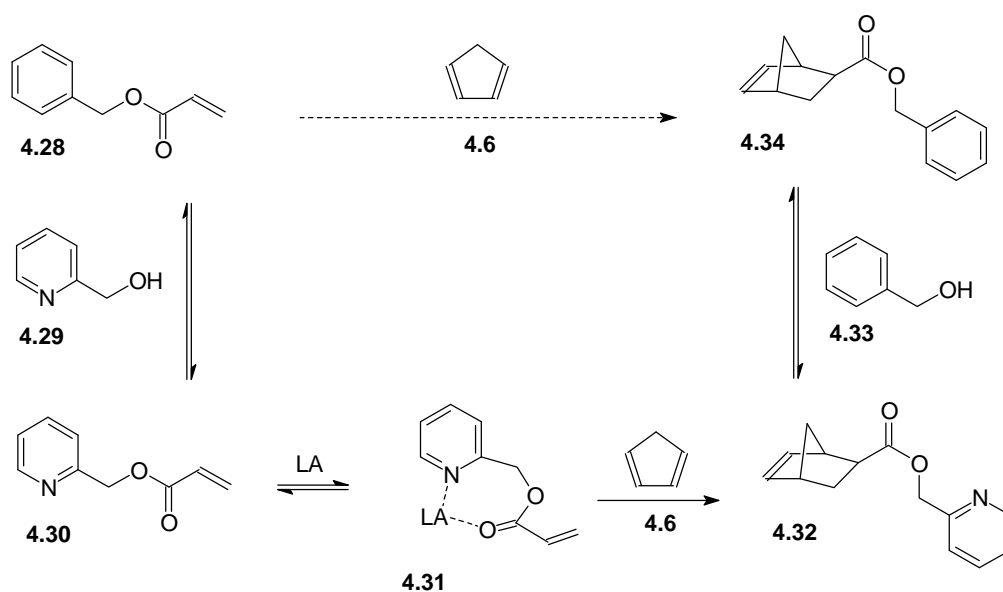
Scheme 4.8.

whereas Section 4.2.3 describes the introduction of an auxiliary via a Mannich reaction.

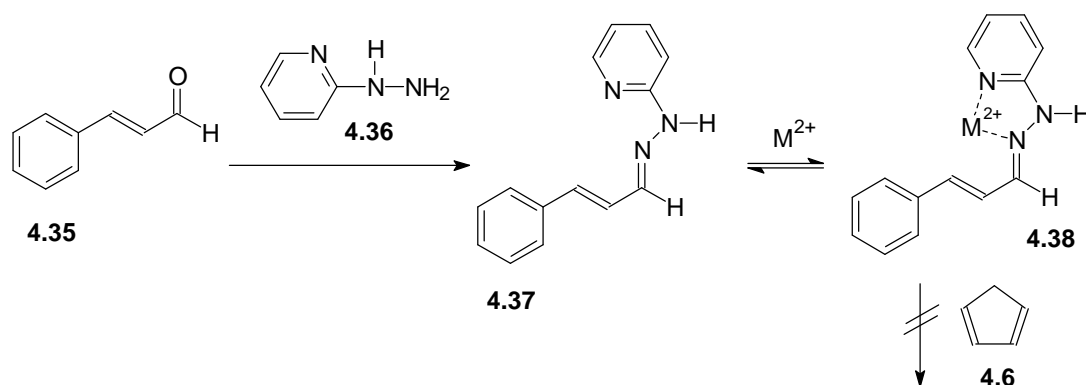
4.2.1 Literature examples of auxiliary-aided catalysis

Some examples of the use of a temporary additional site of coordination have been published. Burk and Feaster¹⁰ have transformed a series of ketones into hydrazones capable of chelating to a rhodium catalyst (Scheme 4.7). Upon coordination, enantioselective hydrogenation of the hydrazone is feasible, yielding N-arylhydrazines in up to 97% ee. Finally, the hydrazines were transformed into amines by treatment with SmI_2 .

Czarnik et al.¹¹ studied the auxiliary-assisted copper(II)-ion catalysed hydrolysis of acrylate esters



Scheme 4.9.



Scheme 4.10.

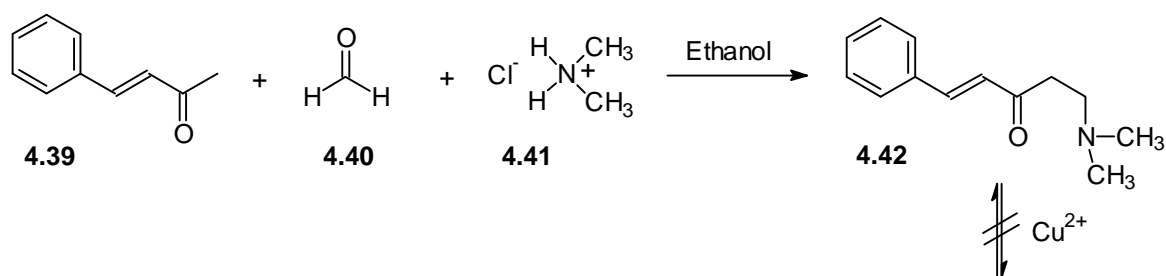
and amides (Scheme 4.8). A chelating diamine was allowed to react in a Michael addition with either an acrylate ester or amine. This reaction led to product **4.24** capable of chelating a copper(II) ion, which serves as a catalyst for the hydrolysis of the ester or amide functionality. Finally the auxiliary was removed by heating an aqueous solution of **4.26** in the presence of copper(II)triflate. Interestingly, no metal-ion promotion of the hydrolysis reactions was observed when monodentate butylmethylamine was used as auxiliary instead of bidentate N-benzyl-N',N'-dimethylethylenediamine (**4.23**).

Westwell and Williams¹² suggested an elegant approach using only a catalytic amount of auxiliary in a Lewis-acid catalysed Diels-Alder reaction (Scheme 4.9). These authors anticipated that in situ transesterification could convert a non-chelating into a chelating dienophile. Coordination to the Lewis-acid catalyst and reaction with the diene, followed by another in situ transesterification step would ultimately result in the desired Diels-Alder adduct **4.34**. Unfortunately, it turned out that the cycle depicted in Scheme 4.9, although elegant, is rather inefficient. Westwell and Williams¹² performed competition experiments to assess the difference in reactivity between **4.28** and **4.30**. In the presence of Lewis-acid catalysts, this difference was invariably smaller than a factor of 10, whereas Lewis-acid catalysis has the potential of inducing accelerations in the order of $10^3 - 10^5$. Apparently, catalysis via formation of a seven-membered chelate ring is not particularly efficient.

4.2.2 (2-Pyridyl)hydrazine as coordinating auxiliary

Inspired by the work of Burk and Feaster¹⁰, we attempted to use (2-pyridyl)hydrazine (**4.36**) as a coordinating auxiliary (Scheme 4.10). Hydrazines generally react efficiently with ketones and aldehydes. Hence, if satisfactory activation of the dienophile can be achieved through coordination of a Lewis acid to the (2-pyridyl)hydrazone moiety in water, Lewis-acid catalysis of a large class of ketone- and aldehyde-activated dienophiles is anticipated. Subsequent conversion of the hydrazone group into an amine functionality has been reported previously by Burk and Feaster¹⁰.

Reaction of cinnamaldehyde **4.35** with (2-pyridyl)hydrazine (**4.36**) yielded the desired hydrazone **4.37**. As anticipated, this compound coordinates readily to copper(II)nitrate in aqueous solution as



Scheme 4.11.

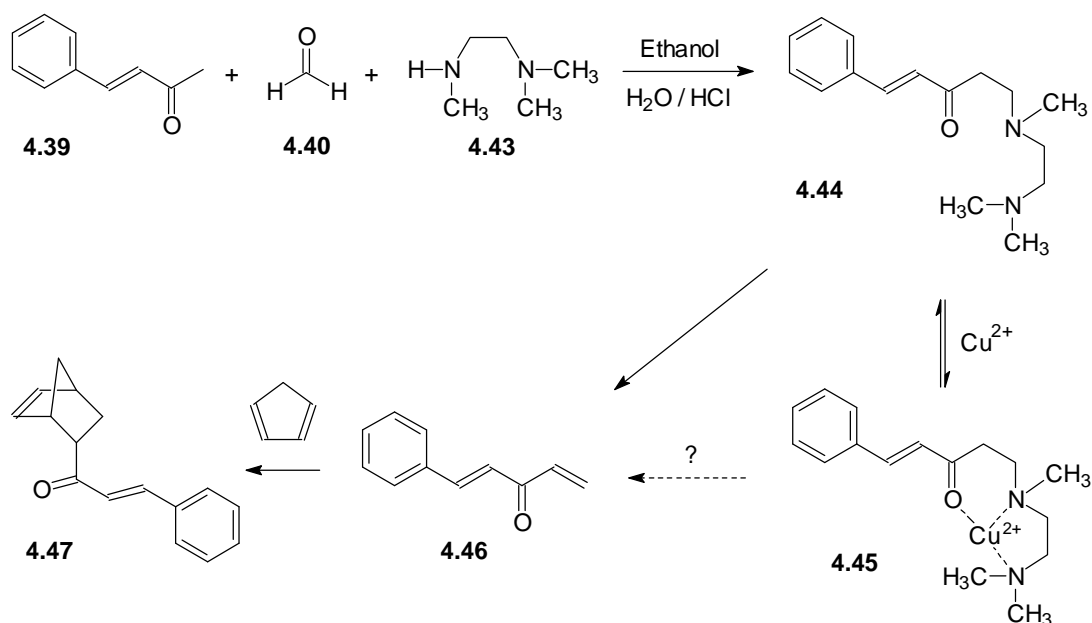
indicated by a shift of the UV absorption band by 17 nm. Unfortunately, subsequent reaction with cyclopentadiene is extremely slow. Apparently, the hydrazone moiety is less capable of transmitting the electron withdrawing influence of the coordinated Lewis-acid than a carbonyl functionality. Hence, (2-pyridyl)hydrazone is not a suitable auxiliary.

4.2.3. A coordinating auxiliary via a Mannich reaction

In a second attempt to extend the scope of Lewis-acid catalysis of Diels-Alder reactions in water, we have used the Mannich reaction¹³ to convert a ketone-activated monodentate dienophile into a potentially chelating β -amino ketone. The Mannich reaction seemed ideally suited for the purpose of introducing a second coordination site on a temporary basis. This reaction adds a strongly Lewis-basic amino functionality on a position β to the ketone. Moreover, the Mannich reaction is usually a reversible process, which should allow removal of the auxiliary after the reaction. Furthermore, the reaction is compatible with the use of an aqueous medium. Some Mannich reactions have even been reported to benefit from the use of water¹⁴. Finally, Lewis-acid catalysis of Mannich-type reactions in mixtures of organic solvents and water has been reported¹⁵. Hence, if both addition of the auxiliary and the subsequent Diels-Alder reaction benefit from Lewis-acid catalysis, the possibility arises of merging these steps into a one-pot procedure.

We chose benzylideneacetone (**4.39**, Scheme 4.11) as a model dienophile for our studies. The uncatalysed Diels-Alder reaction of this compound with cyclopentadiene is slow, justifying a catalytic approach. Reaction of **4.39** with paraformaldehyde and dimethylamine under acidic conditions in an aqueous ethanol solution, following a literature procedure¹⁶, produced the HCl salt of **4.42** (Scheme 4.11). The dienophile was liberated in situ by adding one equivalent of base.

Unfortunately, addition of copper(II)nitrate to a solution of **4.42** in water did not result in the formation of a significant amount of complex, judging from the unchanged UV-vis absorption spectrum. Also after addition of $\text{Yb}(\text{OTf})_3$ or $\text{Eu}(\text{NO}_3)_3$ no indications for coordination were observed. Apparently, formation of a six-membered chelate ring containing an amine and a ketone functionality is not feasible for these metal ions. Note that **4.13** features a similar arrangement and in aqueous solutions, likewise, does not coordinate significantly to all the Lewis acids that have been



Scheme 4.12.

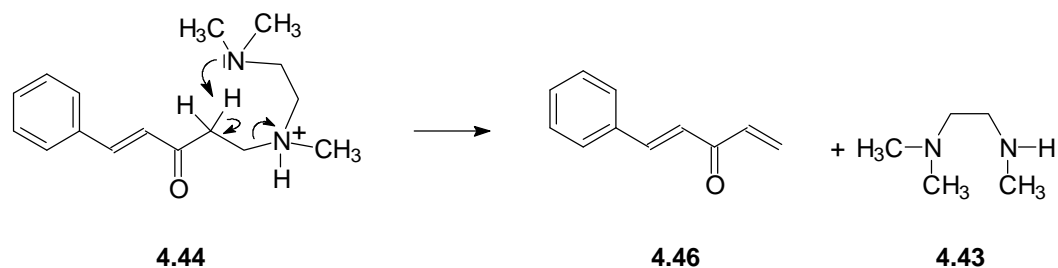
tested.

As anticipated from the complexation experiments, reaction of **4.42** with cyclopentadiene in the presence of copper(II)nitrate or ytterbium triflate was extremely slow and comparable to the rate of the reaction in the absence of Lewis-acid catalyst. Apparently, Lewis-acid catalysis of Diels-Alder reactions of β -amino ketone dienophiles is not practicable.

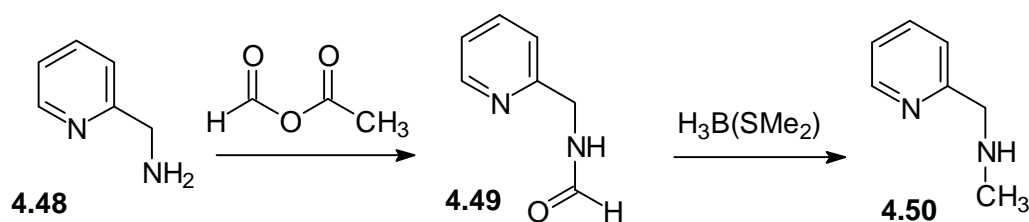
In another attempt to achieve efficient coordination, we have used a strongly chelating diamine (**4.43**) in the Mannich reaction with **4.39** (Scheme 4.12). The reaction was performed in aqueous ethanol, producing **4.44** \cdot 2HCl in 64% yield.

After in situ neutralisation, the complexation behaviour of **4.44** was studied using UV-vis spectroscopy. The absorption maximum of this compound shifted from 294 nm in pure water to 310 nm in a 10 mM solution of copper(II)nitrate in water. Apparently, **4.44**, in contrast to **4.42**, does coordinate to copper(II)nitrate in water.

Unfortunately, **4.44** did not react with cyclopentadiene in the way that was desired. Instead, another reaction occurred, ultimately leading to an unexpected Diels-Alder adduct **4.47** that could be isolated



Scheme 4.13.



Scheme 4.14.

in 68 % yield. Most likely, an intramolecular base-catalysed elimination reaction occurs, producing ketone **4.46** containing a highly reactive terminal vinyl group (Scheme 4.13). This double bond reacts rapidly with cyclopentadiene to give Diels-Alder adduct **4.47**. Most likely no Lewis-acid catalysis is operative in this process.

Note that for **4.42**, in which no intramolecular base catalysis is possible, the elimination side reaction is not observed. This result supports the mechanism suggested in Scheme 4.13. Moreover, at pH 2, where both amine groups of **4.44** are protonated, UV-vis measurements indicate that the elimination reaction is significantly retarded as compared to neutral conditions, where protonation is less extensive. Interestingly, addition of copper(II)nitrate also suppresses the elimination reaction to a significant extent. Unfortunately, elimination is still faster than the Diels-Alder reaction on the internal double bond of **4.44**.

Clearly, the use of diamine **4.43** as a coordinating auxiliary is not successful. However, we anticipated that, if the basicity of the tertiary amine group of the diamine could be reduced, the elimination reaction will be less efficient. We envisaged that replacement of the tertiary amine group in **4.43** by a pyridine ring might well solve the problem.

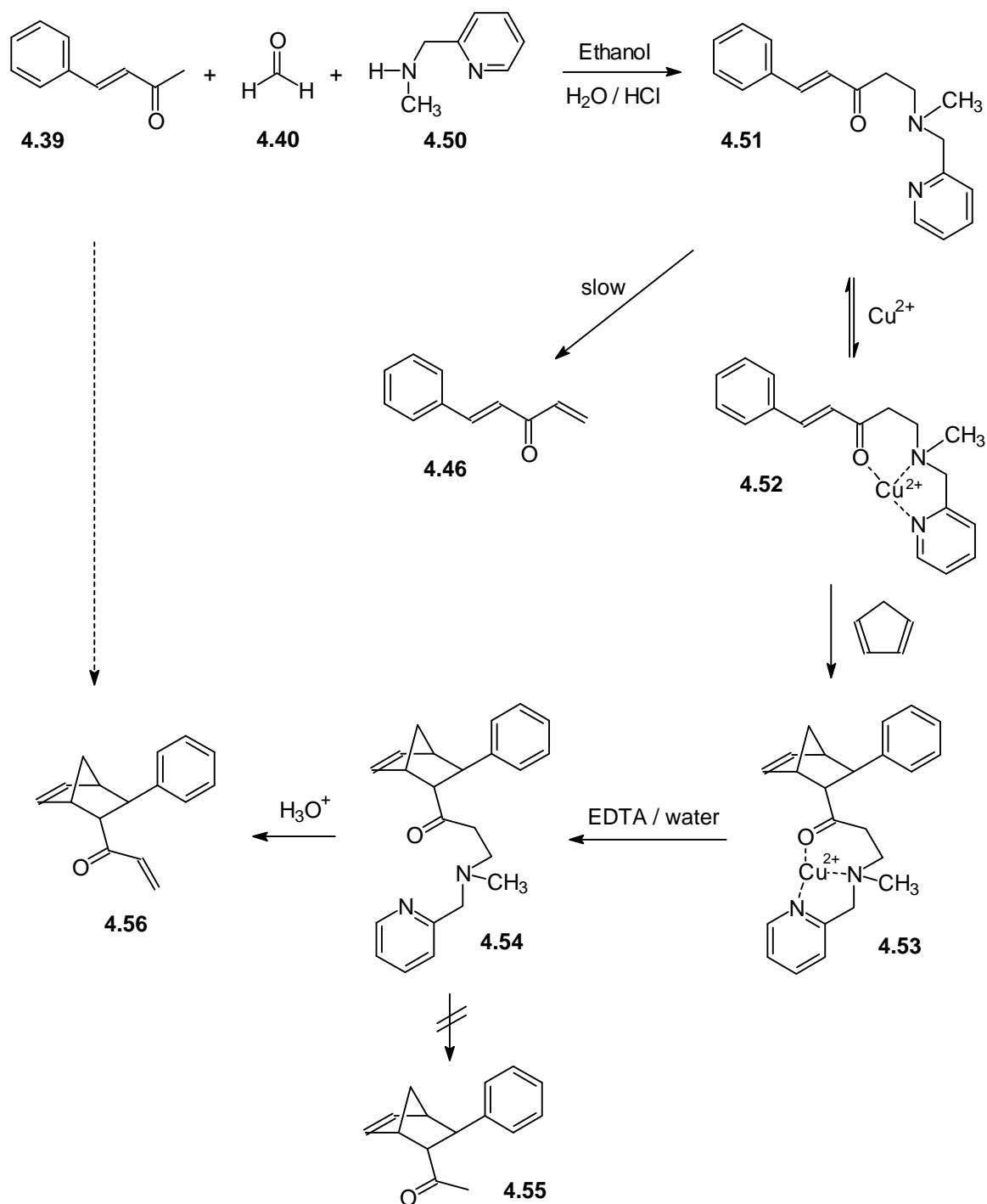
The desired pyridylamine was obtained in 69 % overall yield by monomethylation of 2-(aminomethyl)pyridine following a literature procedure¹⁷ (Scheme 4.14). First amine **4.48** was converted into formamide **4.49**, through reaction with the in situ prepared mixed anhydride of acetic acid and formic acid. Reduction of **4.49** with borane dimethyl sulfide complex produced diamine **4.50**. This compound could be used successfully in the Mannich reaction with **4.39**, affording crude **4.51** in 92 % yield (Scheme 4.15). Analogous to **4.44**, **4.51** also coordinates to copper(II) in water, as indicated by a shift of the UV-absorption maximum from 296 nm to 308 nm.

Most importantly, analysis using UV-spectroscopy also demonstrated that, as anticipated, the elimination reaction of **4.51** is less efficient than that of **4.44**. Again, addition of copper(II)nitrate significantly suppresses this reaction.

Fortunately, in the presence of excess copper(II)nitrate, the elimination reaction is an order of magnitude slower than the desired Diels-Alder reaction with cyclopentadiene, so that upon addition of an excess of cyclopentadiene and copper(II)nitrate, **4.51** is converted smoothly into copper complex **4.53**. Removal of the copper ions by treatment with an aqueous EDTA solution afforded in 71% yield crude Diels-Alder adduct **4.54**. Catalysis of the Diels-Alder reaction by nickel(II)nitrate is also

possible, although it is less efficient than catalysis by copper(II)nitrate. In contrast, Sc(OTf)₃ did not promote this reaction significantly.

Finally, in the last step, the chelating auxiliary had to be removed. Ideally, one would like to convert **4.54** into ketone **4.55** via a retro Mannich reaction. Unfortunately, repeated attempts to accomplish this failed. These attempts included refluxing in aqueous ethanol under acidic and basic conditions and refluxing in a 1:1 acetone - water mixture in the presence of excess paraformaldehyde under acidic conditions, in order to trap any liberated diamine. These procedures were repeated under neutral conditions in the presence of copper(II)nitrate, but without success.



Scheme 4.15.

Apparently, **4.54** is extremely reluctant to undergo a retro Mannich reaction. Riviere¹⁸ demonstrated that this behaviour is not unusual for β -amino ketones. From the study of a large number of Mannich adducts, Riviere concludes that the retro Mannich reaction requires an aromatic group next to the carbonyl functionality. Clearly, **4.54** lacks this arrangement.

Fortunately, under moderately acidic conditions, in the presence of acetone and paraformaldehyde, **4.54** undergoes an elimination reaction similar to that described in Scheme 4.13, producing α,β -

unsaturated ketone **4.56** in 59 % yield. Note that the highly reactive terminal double bond of this compound can be readily employed for other transformations.

The overall yield, if the intermediates are not purified, amounts to 24 %.

In summary, we have demonstrated that it is possible to extend the scope of Lewis-acid catalysis of Diels-Alder reactions in water, by employing a chelating auxiliary. We envisage that analogues of **4.39** capable of undergoing a Mannich reaction with **4.50** can be treated with reactive dienes in the presence of a Lewis-acid catalyst in water.

4.3 Conclusions

Careful examination of literature reporting Lewis-acid catalysis of Diels-Alder reactions in combination with kinetic investigations indicate that bidentate (or multidentate) reactants are required in order to ensure efficient catalysis in water. Moreover, studies of a number of model dienophiles revealed that a potentially chelating character is not a guarantee for coordination and subsequent catalysis. Consequently extension of the scope in this direction does not seem feasible.

Extension of the scope of Lewis-acid catalysis of Diels-Alder reactions in water through the introduction of a temporary chelating auxiliary is possible. With the aid of strongly chelating 2-(N-methylaminomethyl)pyridine (**4.50**), Lewis-acid catalysis of the Diels-Alder reaction of benzylideneacetone (**4.39**) with cyclopentadiene (**4.6**) in aqueous solution is feasible, producing Diels-Alder adduct **4.54**. Unfortunately, removal of the chelating auxiliary from this compound by a retro Mannich reaction was not successful. Instead, an intramolecular base-assisted elimination produced α,β -unsaturated ketone **4.56** in 24 % overall yield. We envisage that other dienophiles that are capable of undergoing a Mannich reaction with **4.50** can be treated with reactive dienes in the presence of a Lewis-acid catalysts in water.

4.4 Experimental section

Materials

(2-Pyridyl)hydrazine (Aldrich), 4-acetylpyridine (Acros), N,N,N'-trimethylethylenediamine (Aldrich), methylrhenium trioxide (Aldrich), InCl₃ (Aldrich), Cu(NO₃)₂·3H₂O (Merck), Ni(NO₃)₂·6H₂O (Merck), Yb(OTf)₃ (Fluka), Sc(OTf)₃ (Fluka), 2-(aminomethyl)pyridine (Acros), benzylideneacetone (Aldrich), and chalcone (Aldrich) were of the highest purity available. Borane dimethylsulfide (2M solution in THF) was obtained from Aldrich. Methyl vinyl ketone was distilled prior to use. Cyclopentadiene was prepared from its dimer immediately before use. (R)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one (**4.15**) has been kindly provided by Prof. H. Hiemstra (University of Amsterdam).

3-Phenyl-1-(4-pyridyl)-2-propene-1-one (4.11)

2.00 g (16.5 mmol) of 4-acetylpyridine and 0.87 g (16.5 mmol) of benzaldehyde were added to 100 ml water at 0-4 °C. The mixture was shaken thoroughly and 10 ml of a 10 % sodium hydroxide solution was added. The reaction mixture was shaken and left overnight undisturbed at 4 °C. Solid **4.11** was collected and washed extensively with water, affording 3.28 g of crude product. Crystallisation from ethanol yielded 1.45 g (6.93 mmol, 42 %) of **4.11**, mp 89.0-89.2. (lit. 87-88°C¹⁹) ¹H-NMR (200 MHz CDCl₃) δ(ppm) = δ 7.44 (d,1H), 7.45 (m,3H), 7.65 (m,2H), 7.77 (m,2H), 7.85 (d,1H), 8.84 (m,2H).

3-Phenylpropenal (2-pyridyl)hydrazone (4.37)

0.50 g (4.6 mmol) of (2-pyridyl)hydrazine (**4.36**) and 0.61g (4.6 mmol) of cinnamaldehyde (**4.35**) were dissolved in a mixture of 5 ml of water of pH 4 (HCl) and 2 ml of ethanol. Solid **4.37** separated overnight upon standing at room temperature. Filtration and crystallisation from ethanol yielded 0.45 g (2.0 mmol, 44 %) of **4.37**, mp. 182.2 - 183.6 °C. ¹H-NMR (300 Mhz, CDCl₃) δ(ppm) = 6.67 (m,2H); 7.02 (m,1H); 7.17 (m,2H); 7.25 (t,2H); 7.36 (d,2H); 7.52 (m,2H); 8.15 (d,1H); 8.96 (s,1H). ¹³C-NMR (300 MHz, CDCl₃) δ(ppm) = 104.89; 113.27; 123.21; 124.17; 125.75; 126.27; 132.95; 134.01; 135.70; 139.02; 144.95; 154.06. Anal. Calcd for C₁₄H₁₃N₃: C, 75.3; H, 5.9; N, 18.8. Found: C, 75.02; H, 6.06; N, 18.5.

1-Dimethylamino-5-phenyl-4-pentene-3-one hydrochloride (4.42·HCl)¹⁶

2.09 g (14.3 mmol) of benzylidene acetone (**4.39**) and 1.17 g (14.3 mmol) of dimethylamine·HCl were added to 5 ml of absolute ethanol. 0.457 g (15.2 mmol) of paraformaldehyde was added and the suspension was refluxed for 15 minutes, resulting in a clear yellow solution. Upon cooling and scratching white solid **4.42·HCl** separated. Crystallisation from ethanol afforded 0.818 g (3.4 mmol, 24%) of **4.42·HCl**, mp 158.4 - 158.7 °C. ¹H-NMR (200 MHz, D₂O) δ(ppm) = 2.80 (s,6H); 3.19 (m,2H); 3.35 (d,2H); 6.75 (d,1H); 7.40(m,3H); 7.56 (m,2H); 7.70 (d,2H). ¹³C-NMR (200 MHz, D₂O) δ(ppm) = 42.63; 52.32; 124.70; 128.53; 128.97; 131.20; 133.59; 145.78; 199.99. Exact mass for **4.42**: calc. 203.131; found 203.131.

1-(N,N-Dimethylaminoethyl)methylamino-5-phenyl-4-pentene-3-one dihydrochloride (4.44·2HCl)

1.46 g (14.3 mmol) of distilled N,N,N'-trimethylethylenediamine (bp. 116-117 °C) was added dropwise to a solution of 3.0 g of concentrated hydrochloric acid in 5 ml ethanol at 0 °C. Subsequently, 0.457 g (15.2 mmol) paraformaldehyde was added, followed by 2.09 g (14.3 mmol) of benzylideneacetone (**4.39**). The reaction mixture was refluxed for 15 minutes. Solid **4.44·2HCl** separated upon cooling. Filtration and washing with cold absolute ethanol afforded 3.06 g (9.20 mmol, 64 %) of **4.44·2HCl**, mp. 183.0-184.8 °C. ¹H-NMR (200 MHz, D₂O) δ(ppm) = 2.81 (s,3H);

2.85 (s,6H); 3.42 (s,4H which exchanged slowly with D); 3.57 (s,4H); 6.70 (d,1H); 7.32 (m,3H); 7.53 (m,2H); 7.59 (d,1H). ^{13}C -NMR (200 MHz, D_2O) $\delta(\text{ppm}) = 40.46; 43.15; 50.13; 50.69; 51.56; 125.58; 128.53; 128.94; 131.23; 133.55; 146.02; 199.74$.

1-(2-Bicyclo[2.2.1]hept-5-enyl)-3-phenylpropene-1-one (4.47)

83 mg (0.25 mmol) of **4.44**·2HCl was added to a solution of 0.61 g (2.5 mmol) of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in 250 ml of water. 100 mg of cyclopentadiene (1.5 mmol) was added after which the flask was sealed carefully and stirred for 24 hours at room temperature. The resulting precipitate was filtered and dried, affording 38 mg (0.17 mmol, 68%) of **4.47**, mp 49.2-49.8. ^1H -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 1.50$ (m,3H); 1.83 (m,1H); 2.91 (s,1H); 3.26 (m, 2H); 5.81 (m,1H); 6.10 (m,1H); 6.83 (d,1H); 7.40 (m,3H); 7.58 (m,3H). ^{13}C -NMR (500 MHz, CDCl_3) $\delta(\text{ppm}) = 27.93; 42.81; 46.11; 49.82; 50.62; 125.26; 128.12; 128.77; 130.14; 134.61; 137.38; 137.42; 141.65; 200.06$.

N-(2-pyridylmethyl)formamide (4.49)

15 g (0.32 mole) of formic acid was added dropwise to 27 g (0.26 mole) of acetic anhydride at 0 °C under a nitrogen atmosphere, after which the mixture was heated to 50-60 °C for 2 hours. The solution was cooled to 0 °C and 20 ml of anhydrous THF was added dropwise, followed by a solution of 8.22 g of 2-aminomethylpyridine (**4.48**) in 40 ml of THF. The reaction was followed by TLC (silicagel / methanol) and was completed after 30 min. The THF was evaporated and the remaining product was purified using bulb to bulb distillation, affording 89% of **4.49**. ^1H -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 4.52$ (d,2H); 7.20 (m,3H); 7.62 (dt,1H); 8.29 (s,1H); 8.50 (d,2H). ^{13}C -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 42.58; 122.41; 122.56; 137.34; 148.38; 155.97; 174.70$. Exact mass: calcd. 136.064; found 136.065.

2-(N-methylaminomethyl)pyridine (4.50)

3.40 g (25 mmole) of **4.49** was dissolved in 80 ml of anhydrous THF at 0 °C under a nitrogen atmosphere. 37.5 ml of a 2M solution of borane dimethylsulfide complex in THF was added dropwise. After the vigorous reaction ceased, the mixture was refluxed. The reaction was monitored with TLC (silicagel / methanol) and was complete in 1.5 hours, after which the reaction mixture was cooled to 0 °C. 25 ml of methanol was added carefully and the mixture was stirred for 1 hour. Hydrogen chloride gas was led through the reaction mixture until an acidic solution was obtained (pH indicator showed a pH < 2). The mixture was refluxed gently for 1 hour. After cooling to room temperature, 50 ml of methanol was added and the solvents were evaporated. The solid residue was treated with a saturated potassium hydroxide solution in water until pH > 12. The solution was extracted three times with 50 ml of ether. The combined ether layers were dried over sodium sulfate and the solvent was evaporated. Bulb to bulb distillation of the residue afforded 2.38 g (19.5 mmol, 78%) of colourless **4.50**. ^1H -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 2.45$ (s,3H); 3.83 (s,2H); 7.11

(t,1H); 7.27 (d,1H); 7.61 (dt,1H); 8.53 (d,1H). ^{13}C -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 35.85; 56.92; 121.72; 122.08; 136.23; 149.14; 159.51$.

1-(2-Pyridylmethyl)methylamino-5-phenyl-4-pentene-3-one dihydrochloride (4.51·2HCl)

0.88 g (7.2 mmol) of **4.50** was added dropwise to a solution of 1.61 g of concentrated hydrochloric acid (16.3 mmol) in 4 ml of ethanol at 0 °C. 1.05 g benzylideneacetone (7.2 mmol) was added, together with 0.23 g (10 mmol) of paraformaldehyde. The suspension was refluxed for 20 minutes, resulting in a clear yellow solution. After cooling to room temperature, 50 ml of ether was added and a yellowish oil separated. The mixture was stirred vigorously for 5 minutes and the ether layer was decanted. The washing procedure was repeated once more. The volatiles were removed in vacuo, resulting in 2.34 g (6.6 mmol, 92%) of crude solid product. Repeated crystallisation from 1-propanol afforded 0.44 g (1.25 mmol, 17%) of **4.51·2HCl** as a white powder, mp 134.1-135.4. ^1H -NMR (200 MHz, D_2O) $\delta(\text{ppm}) = 2.81$ (s,1H); 3.26 (t,2H); 3.47 (t,2H); 4.56 (s,2H); 6.68 (d,1H); 7.32 (m,3H); 7.55 (m,5H); 7.96 (dt, 1H); 8.56 (d,1H). ^{13}C -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 33.43; 40.49; 51.36; 57.97; 124.56; 126.70; 127.73; 128.51; 128.95; 131.23; 133.54; 143.18; 145.47; 145.90; 146.51; 199.66$. Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{OCl}_2$: C, 61.3; H, 6.30; N, 7.95; Cl, 19.9. Found: C, 60.7²⁰; H, 6.43; N, 8.18; Cl, 19.6.

2-(3-((2-Pyridylmethyl)methylamino)1-oxopropyl)-3-phenylbicyclo[2.2.1]hept-5-ene (5.54)

To a solution of 1.93 g (8.00 mmol) $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in 250 ml of water in a 250 ml flask was added 2.70 g (7.67 mmol) of crude **4.51·2HCl**. The solution was adjusted to pH 4.5 (NaOH) and 1.13 g (17 mmol) of cyclopentadiene was added. The flask was sealed carefully and stirred for 3 days during which the clear blue solution changed into a green suspension. The reaction was followed by drawing samples and monitoring the decrease of the absorbance of **4.51** at 300 nm. 2.50 g (8.55 mmol) of EDTA was added and the pH was adjusted to 7. The solution was saturated with NaCl and extracted four times with 250 ml of ether. The combined ether layers were dried over sodium sulfate and the solvent was evaporated, affording 1.62 g (4.68 mmol, 61%) of crude product. After purification by chromatography over silicagel eluting with a 3 : 1 ethanol - ether mixture 0.58 g (1.68 mmol, 22%) of pure **4.56** was obtained as a colourless oil. ^1H -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 1.51$ (d,1H); 1.74 (d,1H); 2.12 (s,3H); 2.57 (m,2H); 2.63 (m,2H); 2.91 (s,1H); 2.99 (m,1H); 3.10 (d,1H); 3.22 (s,1H); 3.53 (s,2H); 5.88 (m,1H); 6.29 (m,1H); 7.14 (m,1H); 7.48 (dt,1H); 8.43 (d,1H). ^{13}C -NMR (200 MHz, CDCl_3) $\delta(\text{ppm}) = 39.52; 42.17; 45.00; 46.31; 47.34; 48.26; 52.14; 60.32; 63.57; 121.87; 122.97; 125.81; 127.34; 128.34; 133.06; 136.31; 139.14; 144.31; 148.98; 158.96; 209.18$.

2-(1-Oxoprop-2-enyl)-3-phenylbicyclo[2.2.1]hept-5-ene (4.56)

169 mg of purified **4.54** (0.488 mmol) was added to 10 ml of water. 0.55 g of paraformaldehyde was added and the mixture was adjusted to pH 1 using diluted hydrochloric acid. 2.5 ml of acetone was added and the reaction mixture was refluxed for 4 hours. Extraction with ether, followed by washing

of the ether layer with brine, drying over sodium sulfate and evaporation of the volatiles, resulted in 81 mg (0.36 mmol, 74%) of crude **4.56**. Chromatography over silicagel eluting with an ether / hexane (20 / 80) mixture afforded 65 mg (0.29 mmol, 59%) of **4.56**. When crude **4.54** was used, the yield after chromatography was 42 %. ¹H-NMR (300 MHz, CDCl₃) δ(ppm) = 1.52 (d,1H); 1.81 (d,2H); 2.95 (s,1H); 3.17 (s,1H); 3.22 (d,2H); 5.62 (dd,1H); 5.88 (m,1H); 6.14 (dd,1H); 6.31 (m,1H); 6.37 (m,1H); 7.17 (m,5H). ¹³C-NMR (300 MHz, CDCl₃) δ(ppm) = 43.10; 44.40; 45.03; 46.16; 55.98; 123.49; 125.97; 125.41; 125.99; 130.82; 132.87; 136.53; 175.01; 197.17. Exact mass: calc.224.119; found 224.120.

Kinetic measurements

Kinetic measurements were performed employing UV-vis spectroscopy (Perkin Elmer λ2, λ5 or λ12 spectrophotometer) using quartz cuvettes of 1 cm pathlength at 25 ± 0.1 °C. Second-order rate constants of the reaction of methyl vinyl ketone (**4.8**) with cyclopentadiene (**4.6**) were determined from the pseudo-first-order rate constants obtained by following the absorption of **4.6** at 253-260 nm in the presence of an excess of **4.8**. Typical concentrations were: [**4.8**] = 18 mM and [**4.6**] = 0.1 mM. In order to ensure rapid dissolution of **4.6**, this compound was added from a stock solution of 5.0 μl in 2.00 g of 1-propanol. In order to prevent evaporation of the extremely volatile **4.6**, the cuvettes were filled almost completely and sealed carefully. The water used for the experiments with MeReO₃ was degassed by purging with argon for 0.5 hours prior to the measurements. All rate constants were reproducible to within 3%.

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- 20 The deviation could be due to the presence of a small amount of water, since **4.51**·2HCl is hygroscopic.

Micellar Catalysis¹

This chapter describes the effects of micelles on the Diels-Alder reaction that was introduced in Chapter 2. In the absence of Lewis-acid catalysts micelles induce modest retardations of this reaction, which is rather surprising in view of the usually high affinity of the Diels-Alder reactants for micellar aggregates. This intriguing lack of reactivity most likely is a result of different average binding locations of diene and dienophile. Evidence from ¹H-NMR shift measurements and paramagnetic-ion induced relaxation rate enhancements is presented. Significantly, in the presence of Lewis-acid catalysts, micelles can induce dramatic rate enhancements, approaching enzyme-like magnitudes. The high rates of the reaction in these media is attributed primarily to an extremely efficient interaction between the dienophile and the Lewis-acid catalyst in the Stern region of the micelle.

5.1 Introduction

“Nonsense McBain !” Those words were the first reaction of the chairman of a meeting of the Royal Society of London on the lecture of McBain, wherein he suggested the existence of assemblies of surfactant molecules in aqueous solution². However, as soon became apparent, McBain was right when he postulated the spontaneous formation of dynamic aggregates by fatty acid salts³, although the bilayer structure he suggested was later corrected by Hartley, who introduced the spherical structures we now know as micelles⁴. In the years that have passed, micellar solutions have proven to be an extremely versatile topic of research. The catalytic potential of micellar aggregates has received special attention. This chapter will focus on micellar catalysis of a Diels-Alder reaction and will provide, for the first time, a link between micellar catalysis and Lewis-acid catalysis. Before elaborating on this, the physical properties and catalytic potential of micellar solutions will be briefly reviewed.

5.1.1 Micellar aggregates: structure and dynamics

Surfactant molecules (also called amphiphiles or detergents) unite a polar or ionic head and a nonpolar tail within the same molecule. The nonpolar 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, at a certain point the solubility limit will be reached 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 will be arrested in an intermediate stage with concomitant formation of aggregates of amphiphilic material, wherein the

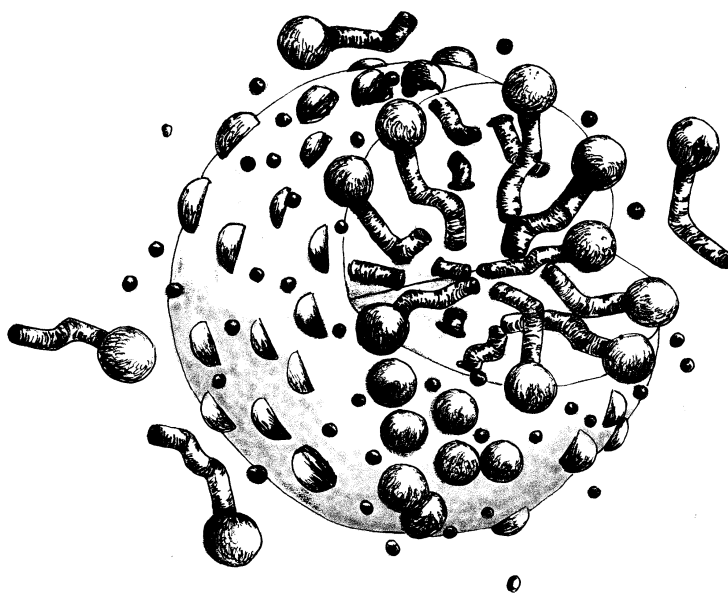


Figure 5.1. Schematic representation of a spherical micelle.

nonpolar parts stick together and are shielded from water, whereas the headgroups are located in the outer regions of the aggregate. A multitude of different aggregates can be formed in this way⁵.

The morphology of these assemblies is mainly determined by the shape of the individual surfactant molecules. Ninham and Israelachvili have introduced the concept of the packing parameter, allowing prediction of the type of aggregate formed by considering the cross-sectional headgroup area and the length and volume of the nonpolar part of the amphiphile molecules⁶. Surfactants containing a single alkyl chain usually form micelles when dissolved in water. A schematic representation of a spherical micelle is given in Figure 5.1. The formation of micelles sets in after a certain critical concentration of surfactant (the critical micelle concentration, *cmc*) has been reached. Beyond this concentration the addition of more surfactant molecules will result in an increase in the number of micelles, while the concentration of monomeric surfactant remains almost constant. Micellisation is usually driven by an increase in entropy, resulting from the liberation of the water molecules from the hydrophobic hydration shells of the monomeric amphiphile molecules, whereas the enthalpy change is generally close to zero⁷.

Micelles are extremely dynamic aggregates. Ultrasonic, temperature and pressure jump techniques have been employed to study the rate constants associated with the different equilibria involved. Rates of uptake of monomers into micellar aggregates are close to diffusion controlled⁸. The residence times of the individual surfactant molecules in the aggregate are typically in the order of $10^5 - 10^6$ seconds^{8,9}, whereas the lifetime of the micellar entity is about $10^{-3} - 10^{-1}$ seconds^{8b,9b}. Factors that lower the *cmc* usually increase the lifetimes of the micelles as well as the residence times of the surfactant molecules in the micelle¹⁰. Due to this dynamic character, the size and shape of micelles are subject to appreciable structural fluctuations. Hence, micellar aggregates are polydisperse, as is demonstrated by small-angle neutron scattering data¹¹. Average aggregation numbers are typically in

the range of 40 - 100¹². The highly dynamic character has for a long time successfully misled chemists in their conception of the structure of a micelle.

Extensive discussions have focused on the conformation of the alkyl chains in the interior¹³. It has been demonstrated that the alkyl chains of micellised surfactant are not fully extended. Starting from the headgroup, the first two or three carbon-carbon bonds are usually *trans*, whereas *gauche* conformations are likely to be encountered near the centre of the chain¹⁴. As a result, the methyl termini of the surfactant molecules can be located near the surface of the micelle, and have even been suggested to be able to protrude into the aqueous phase¹⁵. They are definitely not all gathered in the centre of the micelle as is often suggested in pictorial representations. NMR studies have indicated that the hydrocarbon chains in a micelle are highly mobile, comparable to the mobility of a liquid alkane¹⁶.

Another topic of heated debate comprised the extent of water penetration into the hydrocarbon interior¹³. Small-angle neutron scattering studies have resolved this matter by indicating that significant water penetration into the micellar core is unlikely^{11a,17}. However, at the interface, extensive contact between water and the hydrocarbon chain segments definitely occurs. The headgroups of the micelle are extensively hydrated. For ionic micelles, a large fraction of the counterions are located in the vicinity of the headgroups. These counterions normally retain their first hydration shell¹⁸. The part of the surfactant that contains the headgroups and a variable fraction of the counterions is called the Stern region. This region comprises an appreciable electric field and a high concentration of ions (several molar) at the interface between the nonpolar interior and the aqueous exterior of the micelle and can be expected to exhibit unique properties. For pyridinium iodides the polarity of this region has been probed with the aid of the interionic charge transfer band characteristic for these species. The results indicate a somewhat reduced polarity of the Stern region compared to bulk water¹⁹. The important role of this region in solubilisation and micellar catalysis is reviewed in the next sections.

5.1.2 Solubilisation

One of the most important characteristics of micelles is their ability to take up all kinds of substances. Binding of these compounds to micelles is generally driven by hydrophobic and electrostatic interactions. The dynamics of solubilisation into micelles are similar to those observed for entrance and exit of individual surfactant molecules. Their uptake into micelles is close to diffusion controlled, whereas the residence time depends on the structure of the molecule and the solubilise, and is usually in the order of 10⁻⁴ to 10⁻⁶ seconds^{9b,20}. Hence, these processes are fast on the NMR time scale.

Solubilisation is usually treated in terms of the pseudophase model, in which the bulk aqueous phase is regarded as one phase and the micellar pseudophase as another. This allows the affinity of the solubilise for the micelle to be quantified by a partition coefficient *P*. Different definitions of *P* can be found in the literature, differing in their description of the micellar phase. Frequently *P* is

expressed as a ratio of the mole fractions of solubilisate in the micellar pseudophase and the aqueous phase. However, when dealing with catalysis by micellar aggregates it is more convenient to express P as a ratio of concentrations.

The incorporation of nonionic solutes into micelles has recently been subject to multi-parameter analysis²¹. These studies attribute a dominant role to the volume of the solubilisate in determining the partition coefficient. This suggestion was rationalised on the basis of hydrophobic interactions being more efficient for larger molecules. The hydrogen-bond acceptor capacity of the solubilisate on the other hand counteracted the uptake by the micelles, suggesting that the micellar microenvironment is a less efficient hydrogen-bond donor than bulk water. Still, quantitative understanding of solubilisation is far from complete. For instance, Hirose and Sepulveda have demonstrated that replacement of a proton in the benzene molecule with a hydrophilic group enhances its interaction with the micelle²². The authors attribute this to a shift in the average binding location more towards the surface of the micelle where dipole-dipole interactions are more favourable.

The time-averaged location of different solubilisates in or at the micelle has been a topic of contention²³. The nature of the solubilisate largely determines its position in the aggregate. Saturated hydrocarbons show a preference for the interior of the micelle²⁴. In contrast, solubilisates that contain hydrophilic substituents, such as alcohols or amines, prefer to stay at the surface, where the hydrophilic groups can remain largely hydrated²⁵. In the case that the solubilisate has an amphiphilic character itself, the apolar parts generally are directed towards the centre of the micelle and its orientation in the aggregate resembles that of the surfactant molecules. The position of aromatic hydrocarbons has been intensively debated. Investigations have focused on the distribution of benzene in aqueous solutions of cetyltrimethylammonium bromide (CTAB) and sodium dodecylsulfate (SDS). Some authors have claimed that this solubilisate resides mainly in the interior of these micelles^{22,26}, whereas others have reported data that indicated binding at the interface²⁷ or in both regions simultaneously²⁸. These seemingly contradictory data can be understood in terms of differences in the concentrations of solubilized benzene. At low concentrations these compounds prefer the outer regions of the micelle, whereas at higher concentrations, when the interfacial region is saturated, they penetrate deeper into the micelle with concomitant swelling of the aggregate^{24,29}.

The unexpected preference for the interfacial region at lower concentrations of benzene has prompted speculation. It has been demonstrated that aromatic compounds are capable of forming weak hydrogen bonds with water³⁰. This ability favours uptake in the aqueous interface over solubilisation in the interior. Alternatively, some authors have attributed the binding behaviour of benzene to its weak surface activity that is amplified by the extremely high surface to volume ratio characteristic of micellar solutions³¹. Likewise the high Laplace pressure of small aggregates has been frequently cited as cause^{23,32}. The high pressure in the interior of the small aggregates squeezes out the solubilisate, which then can but bind to the interface. However, as has been pointed out by Marqusee and Dill, the Laplace pressure cannot be the dominant factor, since worm-like and spherical micelles show comparable solubilisation behaviour, whereas the Laplace pressure of the former is half that of the

latter³³. Also the large volume of the interfacial region as compared to the core of the micelle needs to be considered, favouring binding to the interfacial region on purely statistical grounds.

The binding behaviour of benzene can be extrapolated to many other aromatic compounds such as naphthalene and benzene derivatives^{32,34}. Interestingly, a large number of probe molecules contain aromatic rings and many of them will prefer the outer regions of micelles, whereas in bilayer systems, the same molecules prefer the interior of the aggregate³⁵. Clearly these probes cannot be used to determine polarity of the micellar interior or the extent of water penetration therein^{35a}.

For ammonium surfactants there is evidence for the existence of an additional specific interaction between the headgroups of the surfactant and the aromatic solubilise^{22,36}. This is in line with the observation that partition coefficients for benzene in CTAB solutions are much higher than those for SDS solutions^{21a}. These cation- π interactions have been observed in many different fields in chemistry³⁷. The importance of these specific interactions for micellar systems has been questioned by de Schryver et al.³⁸.

5.1.3 Micellar catalysis - kinetic models

A micelle-bound substrate will experience a reaction environment different from bulk water, leading to a kinetic medium effect. Hence, micelles are able to catalyse or inhibit organic reactions. Research on micellar catalysis has focused on the kinetics of the organic reactions involved. An overview of the multitude of transformations that have been studied in micellar media is beyond the scope of this chapter. Instead, the reader is referred to an extensive set of review articles and monographs^{4,6,12,39}.

The kinetic data are essentially always treated using the pseudophase model, regarding the micellar solution as consisting of two separate phases. The simplest case of micellar catalysis applies to unimolecular reactions where the catalytic effect depends on the efficiency of binding of the reactant to the micelle (quantified by the partition coefficient, P) and the rate constant of the reaction in the micellar pseudophase (k_m) and in the aqueous phase (k_w). Menger and Portnoy have developed a model, treating micelles as enzyme-like particles, that allows the evaluation of all three parameters from the dependence of the observed rate constant on the concentration of surfactant⁴⁰.

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 concentration* of the reacting species in or at the micelle. Also for higher-order reactions the pseudophase model is usually adopted (Figure 5.2). However, in these systems the dependence of the rate on the concentration of surfactant does not allow direct estimation of all of the rate constants and partition coefficients involved. Generally independent assessment of at least one of the partition coefficients is required before the other relevant parameters can be accessed. Partition coefficients are usually determined using ultrafiltration⁴¹ or NMR⁴² or UV-vis^{26a} spectroscopy. Kinetics of micelle-catalysed bimolecular reactions are generally monitored spectrophotometrically under pseudo-first-order conditions. The decrease of the absorption of one of the reactants (A) is followed in time in the presence of a more than 20-fold excess of the other

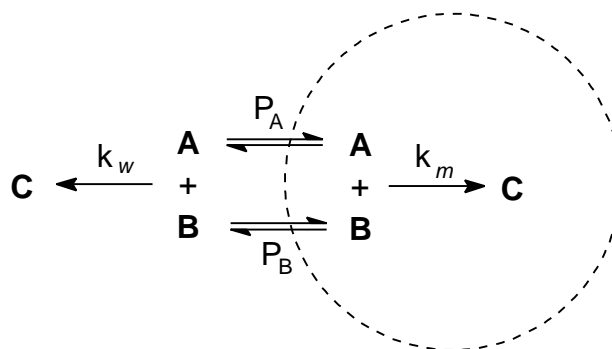


Figure 5.2. Kinetic analysis of a bimolecular reaction $A + B \rightarrow C$ according to the pseudophase model.

reactant (B)⁴³. In the absence of surfactant, the second-order rate constant (k_2) follows from Equation 5.1:

$$k_2 = k_{obs} / [B] \quad (5.1)$$

Herein k_{obs} is the observed pseudo-first-order rate constant. In the presence of micelles, analogous treatment of the experimental data will only provide an apparent second-order rate constant, which is a weighed average of the second-order rate constants in the micellar pseudophase and in the aqueous phase (Equation 5.2).

$$k_{app} = k_{obs} / [B] \quad (5.2)$$

Berezin and co-workers have analysed in detail the kinetics of bimolecular micelle-catalysed reactions^{39c,44}. They have derived the following equation, relating the apparent rate constant for the reaction of A with B to the concentration of surfactant:

$$k_{app} = \frac{k_m P_A P_B [S] V_{mol,S} + k_w (1 + [S] V_{mol,S})}{(1 + (P_A - 1)[S] V_{mol,S})(1 + (P_B - 1)[S] V_{mol,S})} \quad (5.3)$$

Herein P_A and P_B are the micelle - water partition coefficients of A and B, respectively, defined as ratios of the concentrations in the micellar and aqueous phase; $[S]$ is the concentration of surfactant; $V_{mol,S}$ is the molar volume of the micellised surfactant and k_m and k_w are the second-order rate constants for the reaction in the micellar pseudophase and in the aqueous phase, respectively. The appearance of the molar volume of the surfactant in this equation is somewhat alarming. It is difficult to identify the volume of the micellar pseudophase that can be regarded as the potential reaction volume. Moreover, the reactants are often not homogeneously distributed throughout the micelle and

the average location of one reaction partner may differ from that of the other. Despite these serious complications, data analysis using Equation 5.3 almost always produces reasonable results.

Studies of micellar catalysis of bimolecular reactions of uncharged substrates have not been frequent^{41,44,45}. Dougherty and Berg performed a detailed analysis of the kinetics of the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in the presence of anionic and nonionic surfactants⁴¹. Micelles induce increases in the apparent rate constant of this reaction. In contrast, the second-order rate constant for reaction in the micellar pseudophase was observed to be roughly equal to, or even lower than the rate constant in water.

When one or more of the reaction partners of a bimolecular reaction are ionic, the kinetic analysis is further complicated. Particularly in the case when the ionic reactants are not identical to the counterions of the surfactant, estimation of the concentrations of reactive ions in the interfacial region requires a refinement of the model. There is now competition between the reactive counterions and the inert counterions with respect to binding to the micellar surface. Romsted et al. developed the pseudophase ion-exchange (PPIE) model and applied it successfully to the description of the kinetics of micellar catalysis of ionic bimolecular reactions³⁹ⁱ. This model treats the micellar surface as a selective ion exchanger and assumes that the total fractional occupation of the surface by the counterions is constant, irrespective of the nature of these ions. For ionic bimolecular reactions, the second-order rate constant for reaction in the micellar phase is nearly always remarkably similar to the second-order rate constant in the aqueous phase, suggesting a water-like medium for the majority of micelle-catalysed bimolecular reactions^{12,46}. Hence, the frequently encountered increase in the apparent rate constant by several orders of magnitude results largely from the increase in the local concentrations of the reactants in the micellar pseudophase.

5.1.4 The influence of micelles on Diels-Alder reactions

On the basis of the pronounced nonpolar character of the majority of Diels-Alder reactants efficient micellar catalysis of this reaction might be anticipated. Surprisingly, accounts on this topic are scarce. The first report of the influence of surfactants on Diels-Alder reactions stems from 1939, when the BASF company patented the use of detergents for promoting the yields of Diels-Alder reactions in aqueous dispersions⁴⁷. In 1983 Grieco suggested that the high efficiency of the reaction of a surfactant-like diene in aqueous solutions resulted from the formation of micellar aggregates. In the same year Breslow et al. observed a minor retardation of the reaction of cyclopentadiene with a number of dienophiles in solutions of SDS and CTAB as compared to water⁴⁸. Later, other authors obtained similar results for a number of different Diels-Alder reactions⁴⁹. The apparent rate constants of the micelle-catalysed reactions usually significantly exceed those in organic solvents⁵⁰. Interestingly, also modest accelerations in the presence of micellar aggregates compared to the reaction in water have been reported⁵¹.

In summary, all studies on the influence of micelles on bimolecular Diels-Alder reactions indicate that the apparent rate constants in these media are strikingly similar to the rate constants in water.

Unfortunately, more detailed kinetic studies aimed at the determination of the second-order rate constants in the micellar pseudophase have not been published.

Analogously, the effect of micelles on the rate of the unimolecular retro Diels-Alder reaction has been studied. Also here only a modest retardation^{51b} or acceleration^{51c} is observed. Likewise, the presence of micelles has been reported to have a modest influence on an intramolecular Diels-Alder reaction⁵².

Studies on the endo-exo selectivity of a number of different Diels-Alder reactions in micellar media lead to comparable conclusions. Endo-exo selectivities tend to be somewhat smaller in micellar solutions than in pure water, but still are appreciably larger than those in organic media^{48,50a,53}. In contrast, in microemulsions the endo-exo selectivity is reduced significantly^{48,54}.

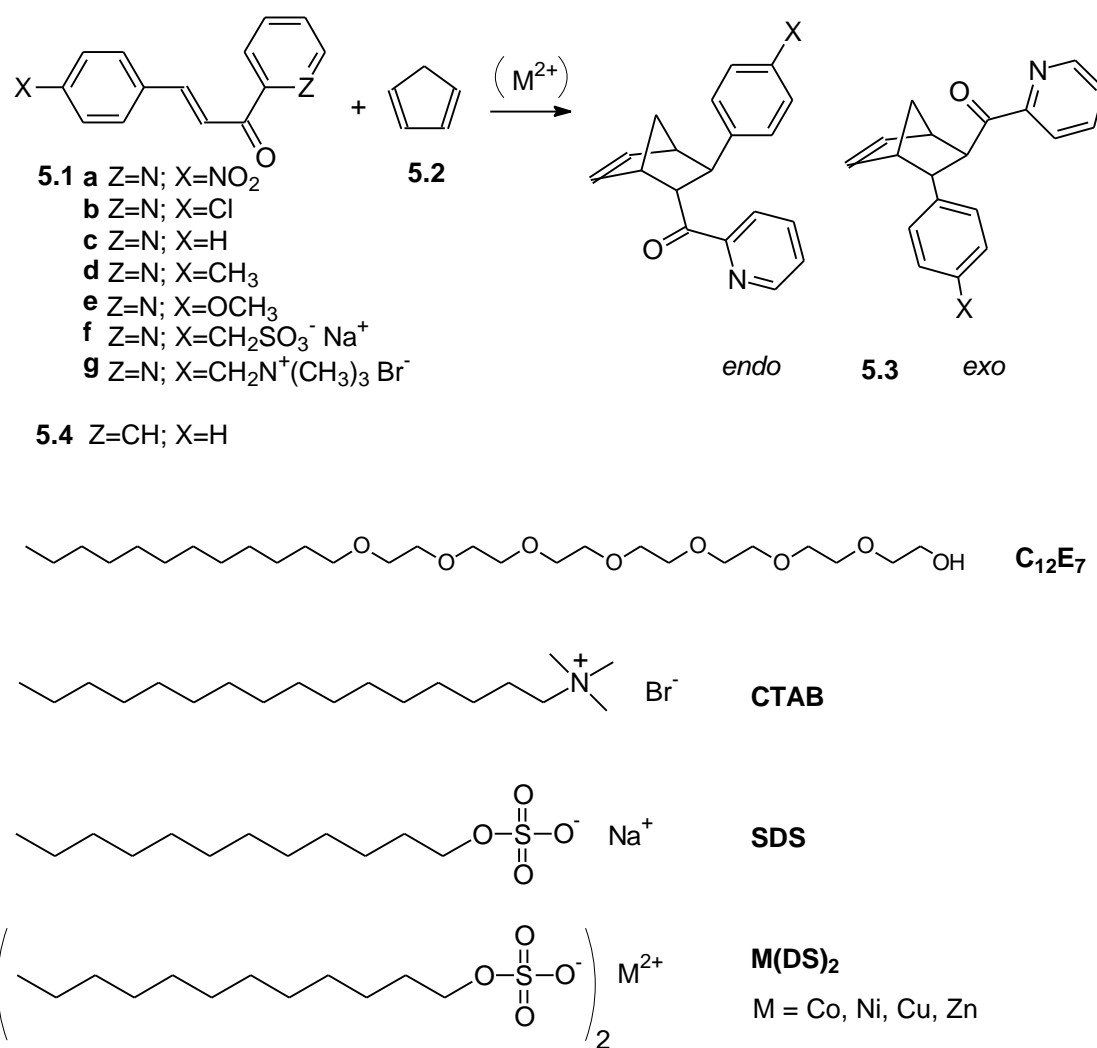
Jaeger and co-workers studied the regioselectivity of the reaction of a surfactant diene with a surfactant dienophile in micellar media⁵⁵. The orientational effects in the aggregates could result in an increase in the regioselectivity in aqueous solutions of these compounds as compared to the reaction in organic media.

It is difficult to extract a consistent molecular picture of the influence of micelles on the Diels-Alder reaction from these rate and selectivity data. On the basis of the pronounced nonpolar character of many of the reactants, one may assume efficient binding of these compounds to micellar aggregates. However, it has been clearly demonstrated that this finding does not give rise to a significant increase in the rate of the reaction. One might argue whether or not this pattern is simply a result of the decreased efficiency of hydrogen bonding interactions and enforced hydrophobic interactions in the micellar aggregates that is compensated by an increased reactant concentration. Following this line of argument, a marked decrease of the rate of the intramolecular and retro Diels-Alder reactions is expected. However, also these processes are barely sensitive to the presence of micellar aggregates. This puzzling situation urged us to undertake a detailed investigation of the effect of micelles on a bimolecular Diels-Alder reaction.

5.2 Results and discussion

This chapter describes the effects of micelles on the Diels-Alder reaction of compounds **5.1 a-g** (see Scheme 5.1) with cyclopentadiene (**5.2**). As far as we know, our study is the first detailed kinetic analysis of micellar catalysis of a Diels-Alder reaction.

The use of dienophile **5.1** also allows study of the effect of micelles on the Lewis-acid catalysed reaction. These studies are described in Section 5.2.2. and represent the first in-depth study of Lewis-acid catalysis in conjunction with micellar catalysis⁵⁶, a combination that has very recently also found application in synthetic organic chemistry⁵⁷.



Scheme 5.1.

5.2.1 Effects of micelles in the absence of Lewis acids

In this section the influence of micelles of cetyltrimethylammonium bromide (CTAB), sodium dodecylsulfate (SDS) and dodecyl heptaoxyethylene ether (C₁₂E₇) on the Diels-Alder reaction of **5.1a-g** with **5.2** in the absence of Lewis-acid catalysts is described (see Scheme 5.1). Note that the dienophiles can be divided into nonionic (**5.1a-e**), anionic (**5.1f**) and cationic (**5.1g**) species. A comparison of the effect of nonionic (C₁₂E₇), anionic (SDS) and cationic (CTAB) micelles on the rates of their reaction with **5.2** will assess of the importance of electrostatic interactions in micellar catalysis or inhibition.

The effect of micelles of SDS, CTAB and C₁₂E₇ on the apparent second-order rate constants of the Diels-Alder reaction between nonionic **5.1a**, anionic **5.1f** and cationic **5.1g** with **5.2** is reported in Table 5.1. These apparent rate constants are calculated from the observed pseudo-first-order rate constants by dividing the latter by the overall concentration of **5.2**.

Table 5.1. Influence of micelles of CTAB, SDS and C₁₂E₇ on the apparent second-order rate constants (M⁻¹s⁻¹) for the Diels-Alder reaction of **5.1a**, **5.1f** and **5.1g**.^(5.4) at 25°C^a.

medium ^b	5.1a	5.1f	5.1g
water	4.02·10 ⁻³	1.74·10 ⁻³	2.45·10 ⁻³
SDS	3.65·10 ⁻³	1.44·10 ⁻³	1.47·10 ⁻³
CTAB	3.61·10 ⁻³	2.83·10 ⁻⁴	2.01·10 ⁻³
C ₁₂ E ₇	3.35·10 ⁻³	1.62·10 ⁻³	2.05·10 ⁻³

^a [5.1] = 2·10⁻⁵ M; [5.2] = 2.0·10⁻³ M ^b All solutions contain 1.0·10⁻⁴ M of EDTA in order to suppress catalysis by trace amounts of metal ions. The concentration of surfactant is 7.8 mM above the *cmc* of the particular compound under reaction conditions (see Appendix 5.1).

$$k_{app} = \frac{k_{obs}}{[5.2]_t}$$

For all entries the concentration of surfactant is 7.8 mM above the *cmc* of the particular compound. The values for the *cmc* have been determined under the particular reaction conditions, and were 3-14 % lower than the *cmc*'s of the pure surfactant (see Appendix 5.1). The rate constants have been obtained by following the decrease of the absorbance of **5.1** employing UV-vis spectroscopic techniques. This technique allows use of very low concentrations of **5.1** of about 2·10⁻⁵ M so that on average there will be not more than one dienophile molecule per micelle. The overall concentration of **5.2** is 2.0 mM, which ensures that, depending on the aggregation number of the surfactant, the average number of cyclopentadiene molecules per micelle varies between 1 and 3⁵⁸. Under these conditions, the effect of micelles on the rate of the Diels-Alder reaction is obviously small and invariably results in a slight *inhibition* of the reaction. The most significant effect occurs for anionic **5.1f** in CTAB solution and for cationic **5.1g** in SDS solution. These are the two combinations for which one would expect essentially complete binding of the dienophile to the micelle as a result of favourable electrostatic interactions in addition to the hydrophobic interactions. Apparently, reaction in the micellar environment is slower than reaction in the bulk aqueous phase, despite the anticipated local increased concentrations of the reactants in the micellar pseudophase. Note that also in the case where electrostatic interactions inhibit binding of the dienophile to the micelle, i.e. **5.1f** in SDS and **5.1g** in CTAB solution, a retardation of the reaction is observed. In these cases the dienophile will most likely reside mainly in the aqueous phase. The retardation will result from a decrease in the concentration of **5.2** in this phase due to its partial solubilisation by the micelles.

In order to interpret the data in Table 5.1 in a quantitative fashion, we analysed the kinetics in terms of the pseudophase model (Figure 5.2). For the limiting cases of essentially complete binding of the dienophile to the micelle (**5.1f** in SDS and **5.1g** in CTAB solution) the following expression can be derived (see Appendix 5.2):

$$\frac{1}{k_{app}} = \frac{[5.2]_t}{k_{obs}} \frac{V_{mol,S}}{k_m} [S] + \frac{V_w}{P_{5.2} V_t k_m} \frac{cmc V_{mol,S}}{k_m} \quad (5.5)$$

Herein $[5.2]_t$ is the total number of moles of **5.2** present in the reaction mixture, divided by the total reaction volume V_t ; k_{obs} is the observed pseudo-first-order rate constant; $V_{mol,S}$ is an estimate of the molar volume of micellised surfactant **S**; k_m and k_w are the second-order rate constants in the aqueous phase and in the micellar pseudophase, respectively (see Figure 5.2); V_w is the volume of the aqueous phase and $P_{5.2}$ is the partition coefficient of **5.2** over the micellar pseudophase and water, expressed as a ratio of concentrations. From the dependence of $[5.2]_t/k_{obs}$ on the concentration of surfactant, $P_{5.2}$ and k_m can be obtained. We used estimates for the molar volume of micellised CTAB⁵⁹ and SDS⁶⁰ of 0.25 M^{-1} and 0.37 M^{-1} , respectively, and assumed $V_w/V_t = 1$, which is reasonable in view of the low concentrations of surfactant used.

Figure 5.3 shows the dependence of the apparent second-order rate constants ($k_{obs}/[5.2]_t$) on the concentration of surfactant for the Diels-Alder reactions of **5.1f** and **5.1g** with **5.2**. The results of the analysis in terms of the pseudophase model are shown in the inset in Figure 5.3 and in the first two

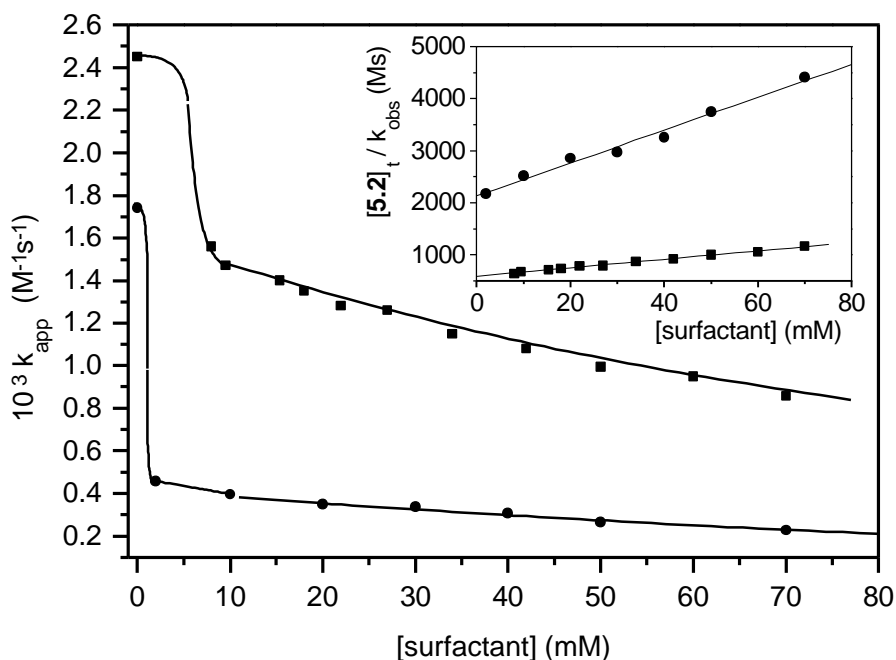


Figure 5.3. Plots of the apparent second-order rate constant, k_{app} ($= k_{obs}/[5.2]_t$) versus the concentration of surfactant for the Diels-Alder reaction of **5.1f** with **5.2** in CTAB solution (■) and of **5.1g** with **5.2** in SDS solution (●) at 25°C. The inset shows the treatment of these data using Equation 5.5. From the slopes and the intercepts $P_{5.2}$ and k_m were calculated (see Table 5.2).

Table 5.2. Analysis using the pseudophase model: partition coefficients for **5.2** over CTAB or SDS micelles and water and second-order rate constants for the Diels-Alder reaction of **5.1f** and **5.1g** with **5.2** in CTAB and SDS micelles at 25°C.

	surfactant	dienophile	k_m ($M^{-1}s^{-1}$) (? 10%)	$P_{5.2}$ (? 10%)
1	CTAB	5.1f	5.9×10^{-6}	68
2	SDS	5.1g	3.1×10^{-5}	61
3	CTAB	5.1g	-	61

entries in Table 5.2.

The reliability of these data depends critically on the validity of the assumptions made in the derivation of Equation 5.5 and on the assumptions underlying the pseudophase model. Also the unavoidable error in the estimation of the volume of the micellar pseudophase that can be regarded as the potential site of binding and reaction will affect the reliability of the results. The system under study offers the possibility of checking the validity of some of the assumptions made during the evaluation of the partition coefficient of **5.2**. By studying the reaction of **5.1f** and **5.1g** with **5.2** in CTAB and SDS solutions, respectively, complete binding of the dienophile to the micelles was assumed. Alternatively, the reaction of **5.1g** with **5.2** in CTAB solution can be studied, in which case the dienophile is assumed to reside exclusively in the aqueous phase. Figure 5.4 shows the dependence of the apparent rate constant of this process on the concentration of CTAB. The kinetics of this process can be described using Equation 5.6 as derived in Appendix 5.3.

$$\frac{1}{k_{app}} \approx \frac{[5.2]_t}{k_{obs}} \approx \frac{P_{5.2} V_{mol,S}}{k_w} [S] + \frac{P_{5.2} cmc V_{mol,S}}{k_w} \approx \frac{V_w}{k_w V_t} \quad (5.6)$$

By plotting the reciprocal of the apparent rate constant versus the concentration of CTAB a straight line is obtained. From the slope of this line and the rate constant in the absence of surfactant (k_w , see Table 5.1) the partition coefficient of **5.2** has been calculated. The result, shown in the third entry in Table 5.2, is in good agreement with the result obtained by the complementary monitoring of the reaction in the micellar phase (entry 1). Apparently treatment according to the pseudophase model as well as the assumption of complete (in case **5.1f**) and negligible (in case of **5.1g**) binding to CTAB micelles is justified. Note that the validity of the estimate of the volume of the micellar pseudophase cannot be judged from these data, since possible errors in this volume will influence the value for the partition coefficient to exactly the same extent in both treatments.

Table 5.2 shows that the partition coefficients of **5.2** over SDS or CTAB micelles and water are similar. Comparison of the rate constants in the micellar pseudophase calculated using the

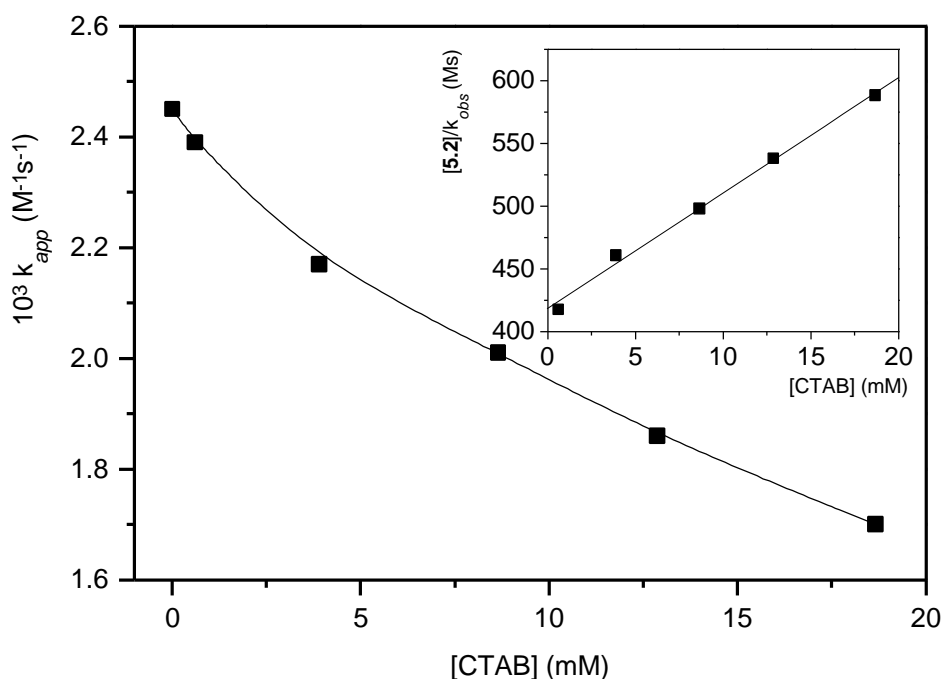


Figure 5.4. Plot of the apparent second-order rate constant, k_{app} ($= k_{obs}/[5.2]_i$) versus the concentration of surfactant for the Diels-Alder reaction of **5.1g** with **5.2** in CTAB solution at 25°C. The inset shows the treatment of these data using Equation 5.6. From slope and intercept $P_{5,2}$ can be calculated (see Table 5.2).

pseudophase model with those in water (Table 5.1) demonstrates a remarkable retardation induced by the micelles. This retardation would suggest that the Diels-Alder reaction experiences a rather apolar medium. This suggestion is in contrast with previous reports that indicate water-like environments for other bimolecular micelle-catalysed reactions. Moreover, **5.1f** and **5.1g** contain ionic moieties, which makes it unlikely that they will be dragged deeply into the micelle.

The Diels-Alder reaction provides us with a tool to probe its local reaction environment in the form of its endo-exo product ratio. Actually, even a solvent polarity parameter has been based on endo-exo ratios of Diels-Alder reactions of methyl acrylate with cyclopentadiene⁶¹ (see also section 1.2.3). Analogously we have determined the endo-exo ratio of the reaction between **5.1c** and **5.2** in surfactant solution and in a number of different organic and aqueous media. These ratios are obtained from the ¹H-NMR of the product mixtures, as has been described in Chapter 2. The results are summarised in Table 5.3, and clearly point towards a water-like environment for the Diels-Alder reaction in the presence of micelles, which is in line with literature observations.

This conclusion seems in conflict with the outcome of the analysis using the pseudophase model. Here we do not speculate on the origins of this discrepancy. Instead, an extensive discussion is provided in Section 5.2.3.

Table 5.3. Endo-exo product ratios of the Diels-Alder reaction of **5.1c** with **5.2** in surfactant solution compared to water and organic solvents.

medium	%endo - %exo
100 mM CTAB	86 - 14
100 mM SDS	88 - 12
100 mM C ₁₂ E ₇	85 - 15
water	84 - 16
ethanol	77 - 23
acetonitrile	67 - 33

5.2.2 Effects of micelles in the presence of Lewis acids

Inspired by the many hydrolytically-active metallo enzymes encountered in nature, extensive studies have been performed on so-called metallo micelles. These investigations usually focus on mixed micelles of a common surfactant together with a special chelating surfactant that exhibits a high affinity for transition-metal ions. These aggregates can have remarkable catalytic effects on the hydrolysis of activated carboxylic acid esters, phosphate esters and amides. In these reactions the exact role of the metal ion is not clear and may vary from one system to another. However, there are strong indications that the major function of the metal ion is the coordination of hydroxide anion in the Stern region of the micelle where it is in the proximity of the micelle-bound substrate. The first report of catalysis of a hydrolysis reaction by metallomicelles stems from 1978⁶². In the years that followed, particularly the groups of Scrimtin and Tonellato⁶³ as well as the groups of Tagaki⁶⁴, Engbersen⁶⁵ and other authors⁶⁶ studied these systems in detail. Apart from catalysing hydrolysis reactions, metallomicelles have also a potential in the complexation of oxygen⁶⁷ and in photochemical processes⁶⁸. Surprisingly, examples of Lewis-acid catalysis by these systems were without precedent at the time we initiated the research described in this chapter.

With the aim of catalysis of the Diels-Alder reaction of **5.1** with **5.2** by metallo micelles, preliminary studies have been performed using the surfactants **5.5a-c**⁶⁹ and **5.6** (Scheme 5.2). Unfortunately, the limited solubility of these surfactants in the pH region that allows Lewis-acid catalysis of the Diels-

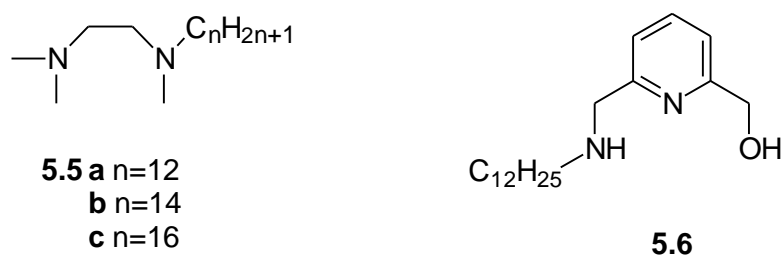
**Scheme 5.2.**

Table 5.4. Apparent second-order rate constants (k_{app}) for the reaction of **5.1c** with **5.2** in micellar solutions^a of Co(DS)₂, Ni(DS)₂, Cu(DS)₂ and Zn(DS)₂ compared to the second-order rate constants (k_2) of the reaction of the corresponding metal ion - **5.1c** complexes^b and the equilibrium constant (K_a) for the complexation of **5.1c** to the corresponding metal ion^b.

metal ion	k_{app} (M ⁻¹ s ⁻¹)	k_2 (M ⁻¹ s ⁻¹)	k_{app} / k_2	K_a (M ⁻¹)
Co ²⁺	0.137	8.40 $\times 10^{-2}$	1.6	1.17 $\times 10^2$
Ni ²⁺	0.152	9.46 $\times 10^{-2}$	1.6	6.86 $\times 10^2$
Cu ²⁺	5.95	2.56	2.3	1.16 $\times 10^3$
Zn ²⁺	0.176	1.18 $\times 10^{-1}$	1.5	7.28 $\times 10^1$

^a The concentration of surfactant was 3.89 mM above the cmc in each case. ^b Values taken from Chapter 2 and determined at a constant ionic strength of 2.0 M using KNO₃ as background electrolyte.

Alder reaction forced us to look for alternative surfactants.

It turned out that the dodecylsulfate surfactants Co(DS)₂, Ni(DS)₂, Cu(DS)₂ and Zn(DS)₂ containing catalytically active counterions are extremely potent catalysts for the Diels-Alder reaction between **5.1** and **5.2** (see Scheme 5.1). The physical properties of these micelles have been described in the literature⁷⁰ and a small number of catalytic studies have been reported. The influence of Cu(DS)₂ micelles on the kinetics of quenching of a photoexcited species has been investigated⁷¹. Interestingly, Kobayashi recently employed surfactants in scandium triflate catalysed aldol reactions⁵⁷. Robinson et al. have demonstrated that the interaction between metal ions and ligand at the surface of dodecylsulfate micelles can be extremely efficient⁷².

In this section the catalytic efficiency of Co(DS)₂, Ni(DS)₂, Cu(DS)₂ and Zn(DS)₂ micelles as well as the effect of CTAB and C₁₂E₇ on the copper-ion catalysed Diels-Alder reaction between **5.1** and **5.2** is described.

The pronounced shift of the UV-vis absorption spectrum of **5.1** upon coordination to a metal ion allows investigation of the complexation behaviour of these compounds in the presence of micelles. Figure 5.5 shows the spectra of nonionic **5.1c** as well as the anionic and cationic counterparts **5.1f** and **5.1g** in water and in surfactant solutions containing copper(II) ions. The shifts of the absorption bands primarily reflect the extent of coordination of the dienophile to the copper ions. Binding to micelles has a negligible influence on the spectrum. Addition of C₁₂E₇ to a 10 mM Cu(NO₃)₂ solution containing the ionic dienophiles **5.1f** and **5.1g** leaves the absorption spectra essentially unchanged. Apparently **5.1f** and **5.1g** have little affinity for C₁₂E₇ micelles. A similar picture emerges for cationic **5.1g**, which resides preferentially in the aqueous phase rather than binding to cationic CTAB micelles. In contrast, **5.1c** has some affinity for C₁₂E₇ and CTAB micelles, resulting in a decreased coordination to the copper ions in the presence of these surfactants. Interestingly, all three

dienophiles, even anionic **5.1f**, bind more efficiently to the copper ions in the presence of $\text{Cu}(\text{DS})_2$ micelles than in a solution containing twice the overall concentration of copper ions. This result is in line with literature observations that revealed an increased interaction between transition-metal ions and chelating organic molecules in the presence of anionic surfactants⁷².

Further evidence for an increased efficiency of complexation in the presence of micellar aggregates with bivalent metal counterions is presented in Table 5.4. The apparent rate constants of the reaction of **5.1c** with **5.2** in the presence of micelles of $\text{Co}(\text{DS})_2$, $\text{Ni}(\text{DS})_2$, $\text{Cu}(\text{DS})_2$ and $\text{Zn}(\text{DS})_2$ are compared to the rate constants for the corresponding bivalent metal ion - dienophile complexes in the absence of micelles. The latter data are not dependent on the efficiency of the formation of the catalyst - dienophile complex whereas possible incomplete binding will certainly be reflected in the former. The good correlations between k_{app} and k_2 and the absence of a correlation between k_{app} and

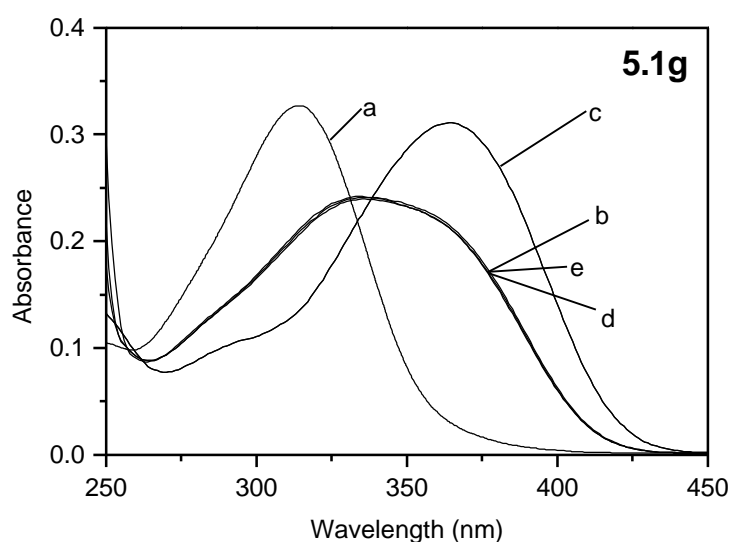
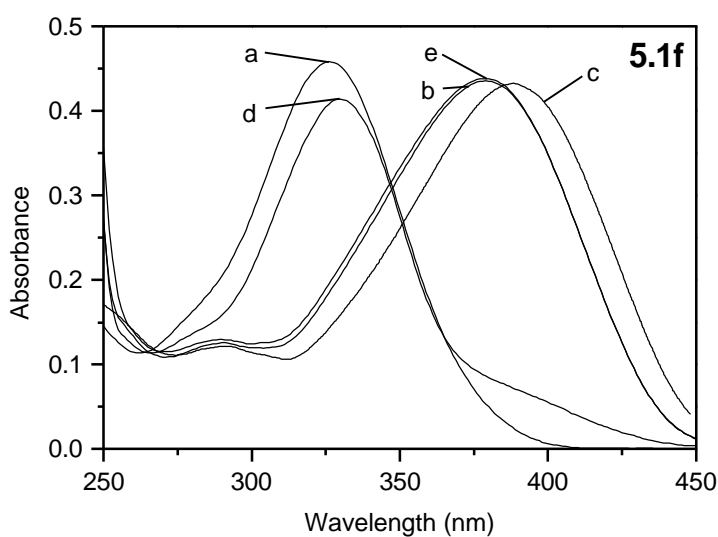
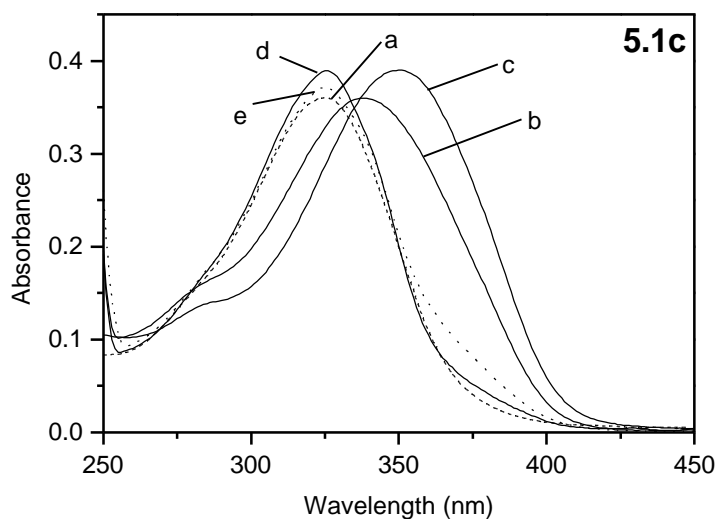


Figure 5.5. UV spectra of **5.1c**, **5.1f** and **5.1g** in water (a) compared to those in solutions containing: 10 mM $\text{Cu}(\text{NO}_3)_2$ (b); 5 mM $\text{Cu}(\text{DS})_2$ (c); 10 mM CTAB plus 10 mM $\text{Cu}(\text{NO}_3)_2$ (d) and 10 mM C_{12}E_7 plus 10 mM $\text{Cu}(\text{NO}_3)_2$ (e).



K_a demonstrate that the equilibrium constant of binding of the dienophile to the metal ion has little influence on the apparent rate constant of the Diels-Alder reaction in the micellar solutions. Hence, we contend that binding of the dienophile to the metal ions is essentially complete in the presence of $M(DS)_2$ micelles.

The enhanced binding predicts a catalytic potential for these solutions and prompted us to investigate the influence of the different types of micelles on the rate of the copper-ion catalysed reaction. Table 5.5 summarises the results, which are in perfect agreement with the conclusions drawn from the complexation studies.

In all surfactant solutions **5.2** can be expected to prefer the nonpolar micellar environment over the aqueous phase. Consequently, those surfactant/dienophile combinations where the dienophile resides primarily in the aqueous phase show inhibition. This is the case for **5.1f** and **5.1g** in C₁₂E₇ solution and for **5.1g** in CTAB solution. On the other hand, when diene, dienophile and copper ion simultaneously bind to the micelle, as is the case for Cu(DS)₂ solutions with all three dienophiles, efficient micellar catalysis is observed. An intermediate situation exists for **5.1c** in CTAB or C₁₂E₇ solutions and particularly for **5.1f** in CTAB solution. Now the dienophile binds to the micelle and is shielded from the copper ions that apparently prefer the aqueous phase. This results in an overall retardation, despite the possible locally increased concentration of **5.2** in the micelle.

Clearly, very promising results were obtained for the Cu(DS)₂ solutions. We have analysed this system in some detail. Figure 5.6 shows the dependence of the rate of the Diels-Alder reaction of **5.1c**, **5.1f**, and **5.1g** with **5.2** on the concentration of Cu(DS)₂. For all three dienophiles the apparent second-order rate constant for their reaction with **5.2** increases dramatically when the concentration of Cu(DS)₂ reaches the *cmc* (1.11 mM). Beyond the *cmc*, the dependence of the rate on the surfactant concentration is subject to two counteractive influences. At higher surfactant concentration, a larger fraction of dienophile will be bound to the micelle, where it reacts faster than in bulk water, resulting in an increase in the rate of the reaction. At the same time, the concentration of diene in the micellar pseudophase will drop with increasing surfactant concentration, due to the increase in the volume of the micellar pseudophase. At higher surfactant concentrations the dienophile will be nearly completely bound to the micelles and the dilution effect will dominate the behaviour. Together, these two effects result in the appearance of a rate maximum at a specific concentration of surfactant that is typical for micelle-catalysed bimolecular reactions. The position of the maximum depends primarily on the micelle-water partition coefficient of the dienophile. For instance, cationic **5.1g** reacts fastest almost at the *cmc*, because of its very high affinity for the anionic Cu(DS)₂ micelles.

Table 5.5. Influence of micelles of Cu(DS)₂, CTAB and C₁₂E₇ on the apparent second-order rate constants (M⁻¹s⁻¹) for the copper(II) catalysed Diels-Alder reaction of **5.1c**, **5.1f** and **5.1g** with **5.2** at 25°C^a.

medium	5.1c	5.1f	5.1g
10 mM Cu(NO ₃) ₂	1.11	1.38	2.13
5 mM Cu(DS) ₂	5.95	5.50	15.3
CTAB ^b + 10 mM Cu(NO ₃) ₂	0.401	0.150	1.84
C ₁₂ E ₇ ^b + 10 mM Cu(NO ₃) ₂	0.630	1.08	1.71

^a [1] = 2.7·10⁻⁵ M; [2] = 1.0·10⁻³ M ^b The concentration of surfactant is 3.89 mM above the *cmc* ^c The concentration of surfactant is 7.8 mM above the *cmc* of the particular compound under the reaction conditions.

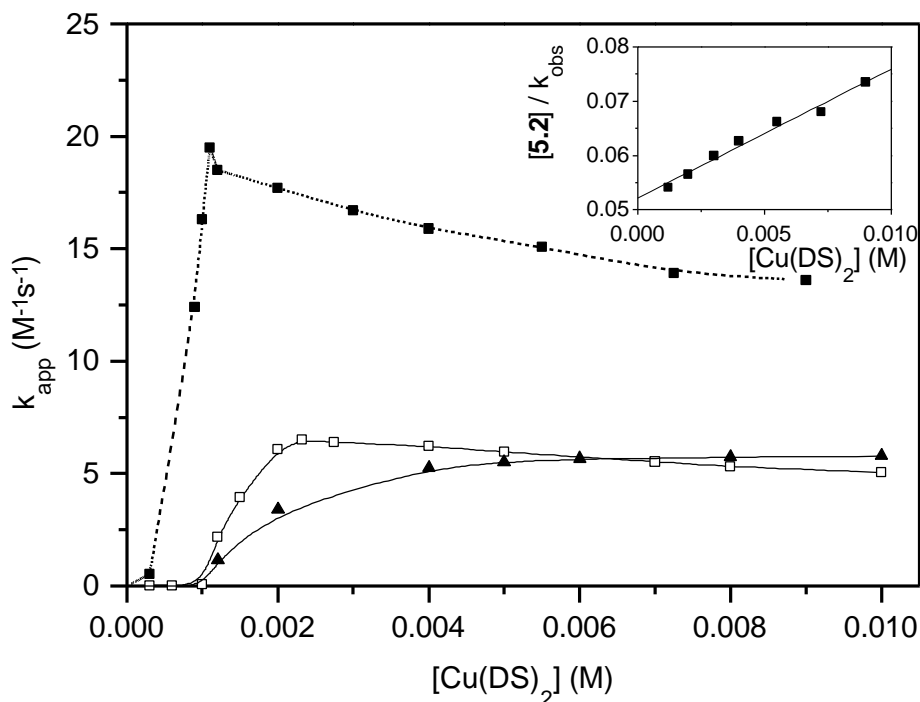


Figure 5.6. Plots of the apparent second-order rate constant (k_{app}) versus the concentration of $\text{Cu}(\text{DS})_2$ for the Diels-Alder reaction of **5.1c** (□), **5.1f** (▲) and **5.1g** (■) with **5.2** at 25°C. The inset shows the treatment of the data for the reaction of **5.1g** according to the pseudophase model.

Formation of a complex with a copper cation only further stimulates this behaviour. As a result, **5.1g** is almost completely bound to the micelles, even at low concentrations of $\text{Cu}(\text{DS})_2$. By contrast, the reaction of **5.1f** still benefits from an increasing surfactant concentration at 10 mM of $\text{Cu}(\text{DS})_2$. In fact, it is surprising that the reaction of this anionic compound is catalysed at all by an anionic surfactant. Probably it is the copper complex of **5.1f**, being overall cationic, that binds to the micelle. Not surprisingly, the neutral substrate **5.1c** shows intermediate behaviour.

Interestingly, at very low concentrations of micellised $\text{Cu}(\text{DS})_2$, the rate of the reaction of **5.1a** with **5.2** was observed to be zero-order in **5.1a** and only depending on the concentration of $\text{Cu}(\text{DS})_2$ and **5.2**. This is akin to the turn-over and saturation kinetics exhibited by enzymes. The acceleration relative to the reaction in organic media in the absence of catalyst, also approaches enzyme-like magnitudes: compared to the process in acetonitrile (Chapter 2), $\text{Cu}(\text{DS})_2$ micelles accelerate the Diels-Alder reaction between **5.1a** and **5.2** by a factor of 1.8×10^6 . This extremely high catalytic efficiency shows how a combination of a beneficial aqueous solvent effect, Lewis-acid catalysis and micellar catalysis can lead to tremendous accelerations.

The essentially complete binding of **5.1g** to the Cu(DS)₂ micelles allows treatment of the kinetic data of Figure 5.6 using the pseudophase model. Since it is very likely that **5.1g** binds in the Stern region (vide infra), complete binding to the copper ions can be assumed. Using Equation 5.5, the Cu(DS)₂ - water distribution coefficient of **5.2** is obtained as well as the second-order rate constant for reaction in the micellar pseudophase (see inset in Figure 5.6). Unfortunately no literature data exist for the molar volume of Cu(DS)₂ that is required for the kinetic analysis. We have used an estimate of the molar volume of micellised Cu(DS)₂ of 0.50 M⁻¹, twice as large as the number that we have used previously for SDS⁷³.

Calculations using this value afford a partition coefficient for **5.2** of 96 and a micellar second-order rate constant of 0.21 M⁻¹s⁻¹. This partition coefficient is higher than the corresponding values for SDS micelles and CTAB micelles given in Table 5.2. This trend is in agreement with literature data, that indicate that Cu(DS)₂ micelles are able to solubilize 1.5 times as much benzene as SDS micelles^{70a}. Most likely this enhanced solubilisation is a result of the higher counterion binding of Cu(DS)₂

Table 5.6. Hammett ρ -values for the copper(II)-catalysed Diels-Alder reaction of **5.1a-e** with **5.2** in different media.

medium	ρ
10 mM Cu(DS) ₂	0.86
10 mM Cu(NO ₃) ₂ in acetonitrile	0.96 ^b
10 mM Cu(NO ₃) ₂ in ethanol	1.00 ^b
10 mM Cu(NO ₃) ₂ in water ^a	0.82 ^b

^a Ionic strength 2.00 M (KNO₃). ^b Data taken from Chapter 2.

micelles (89% versus 60%, see Appendix 5.1), which reduces headgroup repulsion and allows a tighter packing of the headgroups resulting in decreased water penetration and an increased nonpolar character of the micellar interior as compared to SDS micelles.

Comparison of the micellar second-order rate constant of 0.21 M⁻¹s⁻¹ with the rate constants for the reaction in acetonitrile (0.472 M⁻¹s⁻¹) and ethanol (0.309 M⁻¹s⁻¹), again points to a relatively apolar medium for the Diels-Alder reaction. This conclusion is hard to reconcile with the ionic character of two of the three reaction partners involved.

In order to obtain more insight into the local environment for the catalysed reaction, we investigated the influence of substituents on the rate of this process in micellar solution and compared this influence to the corresponding effect in different aqueous and organic solvents. Plots of the logarithms of the rate constants versus the Hammett ρ -value show good linear dependences for all

media. The resulting ρ -values are shown in Table 5.6. The ρ -value in $\text{Cu}(\text{DS})_2$ solution resembles that in aqueous solution more than those in organic solvents.

It appears that the outcome of the analysis using the pseudophase model is not in agreement with experimental observations. Apparently, one (or more) of the assumptions of the pseudophase model is not valid for the system studied here. In particular, the treatment of the micellar pseudophase as a homogeneous “solution” might not be warranted. Therefore we contend that diene and dienophile, on average, reside in different parts of the micelle. Surely, this would impede the reaction. This arrangement would also explain the absence of a large catalytic effect in cases where diene and dienophile bind efficiently to the micelle. In order to check this hypothesis, we probed the binding sites of diene and dienophile using ^1H -NMR techniques.

5.2.3 Average binding sites and their implications

NMR methods have been regularly employed in the study of micellar solutions⁷⁴. The most frequently encountered technique to probe the binding location of aromatic compounds in micelles makes use of changes in the chemical shifts in the ^1H -NMR spectrum of the surfactant induced by the ring current of the aromatic moiety of the solubilisate^{27a,34c,35a,75}. In general, protons located above or below the plane of the aromatic ring are shielded and, hence, experience upfield shifts. Protons in plane with the aromatic ring, on the other hand, are deshielded and shift downfield. In the absence of any specific interactions or orientational constraints, the shielding effect of the aromatic ring of one compound on the proton chemical shifts of another is dominant and results in an upfield shift⁷⁶. Note that any preference for a specific orientation is reflected in the magnitude of the ring-current induced shifts. Consequently, interpretation of shift data in terms of binding locations is somewhat hazardous.

Studies on a large number of aromatic compounds have revealed that for CTAB the largest shift occurs for the alkyl chain protons near the surfactant headgroup, whereas in SDS nearly all proton signals are shifted significantly^{75b-e}. For SDS, the most pronounced shifts are observed for protons around the centre of the chain. This result has been interpreted in terms of deeper penetration of aromatic compounds into SDS micelles relative to CTAB micelles^{75b-e}.

The aromatic shifts that are induced by **5.1c**, **5.1f** and **5.1g** on the ^1H -NMR spectrum of SDS, CTAB and $\text{Zn}(\text{DS})_2$ have been determined. $\text{Zn}(\text{DS})_2$ is used as a model system for $\text{Cu}(\text{DS})_2$, which is paramagnetic. The *cmc*s and counterion binding for $\text{Cu}(\text{DS})_2$ and $\text{Zn}(\text{DS})_2$ are similar and it has been demonstrated in Chapter 2 that $\text{Zn}(\text{II})$ ions are also capable of coordinating to **5.1**, albeit somewhat less efficiently than copper ions. Figure 5.7 shows the results of the shift measurements. For comparison purposes also the data for chalcone (**5.4**) have been added. This compound has almost no tendency to coordinate to transition-metal ions in aqueous solutions. From Figure 5.7 a number of conclusions can be drawn. (1) The shifts induced by **5.1c** on the NMR signals of SDS and CTAB

show the characteristics usually observed for benzene derivatives. Comparison of the shifts induced by **5.1c** on the proton resonances of CTAB with dodecyltrimethylammonium bromide (Figure 5.7j) demonstrates that the differences between SDS and CTAB with respect to the solubilisation of **5.1c** are only partly due to a difference in chain length. There seems to be an intrinsic difference between the interaction of the sulfate and the ammonium headgroup with the aromatic solubilisate, in line with literature evidence for a specific cation - arene interaction (see Section 5.1.2). (2) Introduction of an ionic group in the dienophile (compare Figure 5.7e with 5.7h and 5.7f with 5.7i) causes this compound to reside on average closer to the headgroups of the surfactant. (3) Chelation of the dienophile to a zinc(II) ion has little effect on its location in the micelle (compare Figure 5.7a with 5.7d). (4) The presence of the pyridine nitrogen atom influences the binding location only to a minor extent (compare Figure 5.7b with 5.7e and 5.7c with 5.7f).

Figure 5.7k shows the shifts of the proton signals of C₁₂E₇ as induced by **5.1c**. All parts of the surfactant experience an appreciable shift. The strongest shifts are observed near the interface between the alkyl chains and the ethyleneoxide part, suggesting that **5.1c** prefers the interfacial region of the nonionic micelles.

Surprisingly, the shifts observed in the NMR spectrum of Zn(DS)₂ as caused by **5.1g** seem to point towards a relatively deep penetration of this compound into the micelle, which is extremely unlikely. **5.1g**, when bound to Zn(DS)₂ micelles, will coordinate to a Zn(II) ion. The resulting complex will now have three positive charges: two of the zinc ion at one end of the complex and one of the trimethylammonium group at the other end. It is hard to imagine that this very hydrophilic complex will penetrate into the micellar interior. Still the shifts indicate a short distance between the n-protons⁷⁷ of the surfactant and the aromatic rings of **5.1g**. The most likely explanation for this behaviour, is bending of the alkyl chain of the surfactant towards the aromatic parts of the dienophile. This demonstrates that an interpretation of shift data solely in terms of depth of penetration into the micelle is hazardous. The observed shifts of surfactant protons merely indicate a proximity of aromatic groups and, strictly, do not provide direct information about the location where this encounter occurs. Still, from the data in Figure 5.7 it may be concluded that, on average, the dienophile is not in the core of the micelle.

In a second attempt to obtain more insight into the binding location of the dienophile and now also the diene, we have made use of the influence of paramagnetic ions on the spin-lattice relaxation rates of species in their proximity. Close to these ions the spin-lattice relaxation rate is dramatically enhanced. This effect is highly distance-dependent as is expressed by Equation 5.7, describing the spin-lattice relaxation time in the absence of inner-sphere coordination⁷⁸.

$$\frac{1}{T_1} \approx \frac{D}{d^6} \frac{6^2 \tau_s}{1 + \tau_s^2} \approx \frac{14 \tau_s}{1 + \tau_s^2} \quad (5.7)$$

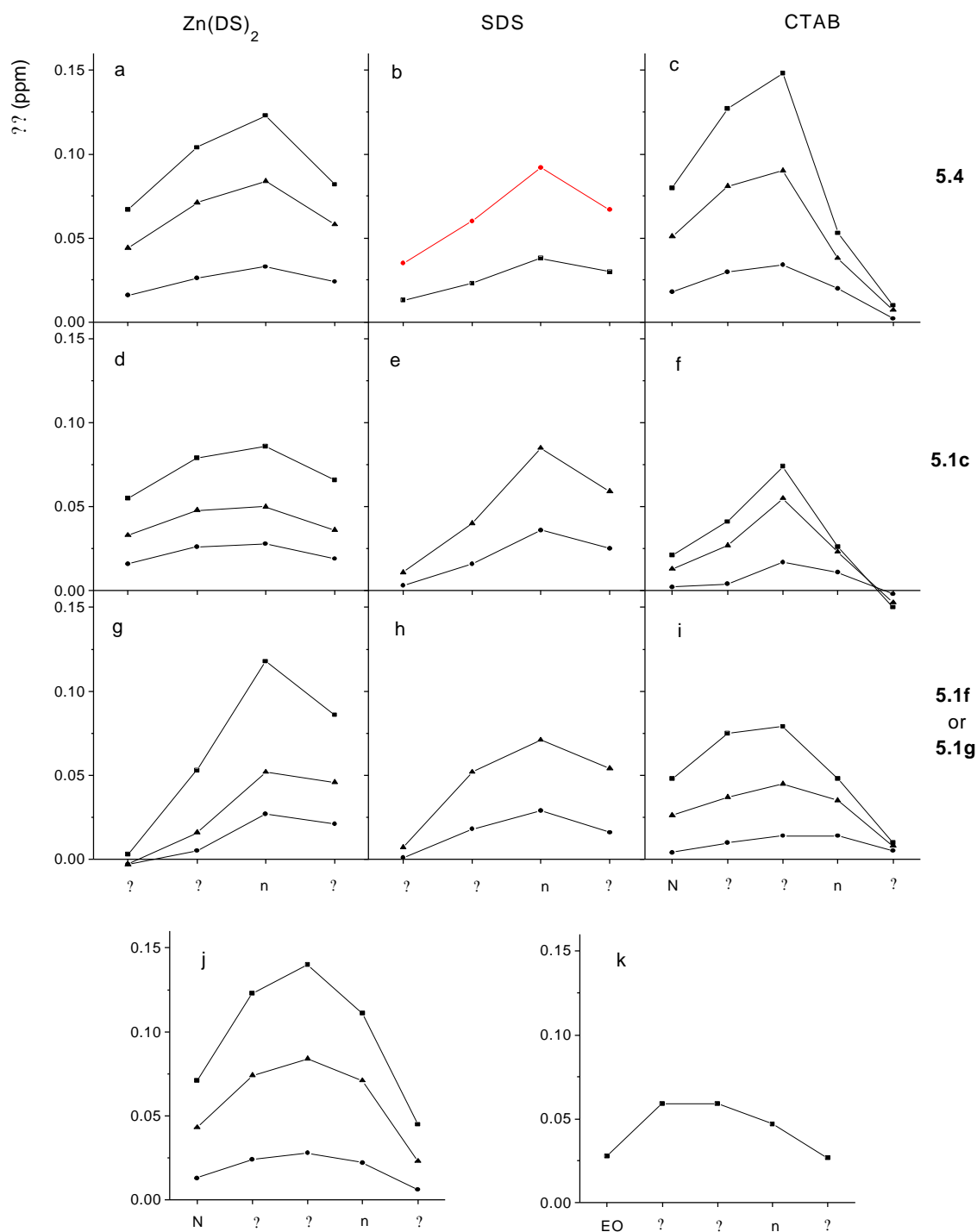


Figure 5.7. Aromatic solubilisate-induced changes in the chemical shifts (upfield) of the ^1H -NMR signals of micellised surfactant. Figures a-f show the effect of 5.4 and 5.1c on the proton resonances of $\text{Zn}(\text{DS})_2$ (25 mM), SDS (50 mM) and CTAB (50 mM). Figure g and h show the corresponding effect of 5.1g on $\text{Zn}(\text{DS})_2$ (25 mM) and SDS (50 mM), respectively. Figure i depicts the effect of 5.1f on the CTAB (50 mM) resonances. Figure j shows the shifts induced by 5.1c on the DTAB (50 mM) resonances and Figure k the corresponding effect on C_{12}E_7 (50 mM). The concentrations of the solubilisate were 2.0 (■), 5.0 (▲) or 8 (●) mM. N stands for the protons at the three headgroup methyl moieties of CTAB, ? and ? for the methylene protons at the ? and ? positions relative to the headgroup. ? represents the terminal methyl group protons and n the protons between the ? and ? positions.

Here T_1 is the spin-lattice relaxation time due to the paramagnetic ion; d is the ion-nucleus distance; D is a constant related to the magnetic moments, ω_1 is the Larmor frequency of the observed nucleus and ω_s is the Larmor frequency of the paramagnetic electron and τ_s its spin relaxation time.

Paramagnetic relaxation techniques have been employed in investigations of the hydrocarbon chain conformation of micellised surfactant^{78,79}, in estimations of the viscosity of the micellar surface⁸⁰ and of the counterion binding⁸¹ and in solubilisation studies^{42,75d,e,82}. Generally, one can select the charge of the paramagnetic ion so that it will be a counterion to the micellar system under study, which ensures that it will be located primarily in the Stern region of the micelle. Consequently, compounds bound to the outer regions of the micelle will experience a much larger influence of these paramagnetic ions than compounds located in the interior of the micelle. The relaxation rate induced by the paramagnetic ion (r_p) can be assessed by subtracting the observed relaxation rates in the absence of these ions from those obtained in the presence of the paramagnetic species. The exact magnitude of r_p is strongly dependent upon the local concentration of the paramagnetic ions at the micelle. Consequently, normalisation of the r_p values is required before comparisons between separately prepared solutions can be made. Hence, throughout this study the r_p values will be expressed as a percentage of the r_p value of the methylene group next to the surfactant headgroup.

We have used the paramagnetic relaxation technique to study the binding locations of **5.1c**, **5.1f**, **5.1g** and **5.2** in CTAB, SDS and $Zn(DS)_2$ solutions, employing $[Cu(EDTA)]^{2-}$, Cu^{2+} (for **5.2**) or Dy^{3+} (for **5.1**) as paramagnetic species. Figure 5.8 shows the values of r_p for **5.1c** and **5.1f** in CTAB solution

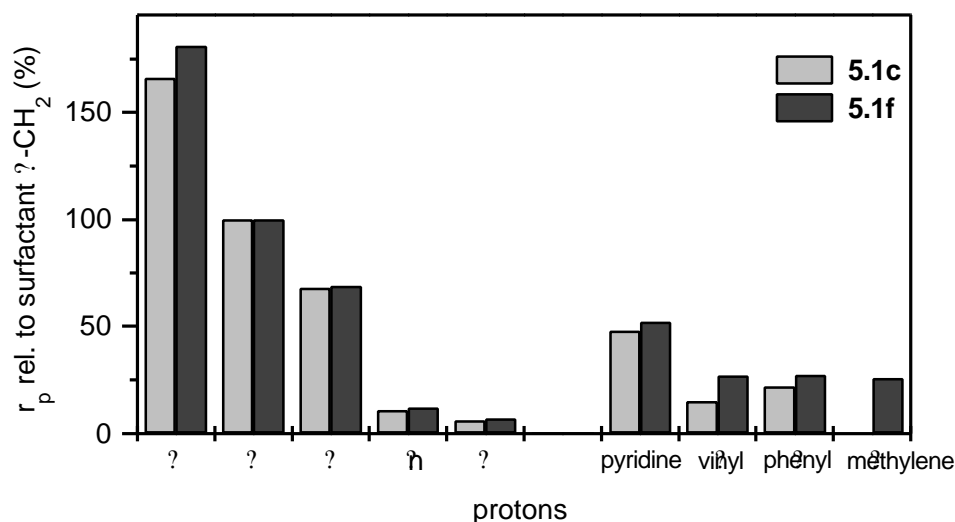


Figure 5.8. Paramagnetic ion-induced spin-lattice relaxation rates (r_p) of the protons of **5.1c** and **5.1f** in CTAB solution and of CTAB in the presence of **5.1c** or **5.1f**, normalised to r_p for the surfactant $-CH_2$. The solutions contained 50 mM of CTAB, 8 mM of **5.1c** or **5.1f** and 0 or 0.4 mM of $[Cu(EDTA)]^{2-}$.

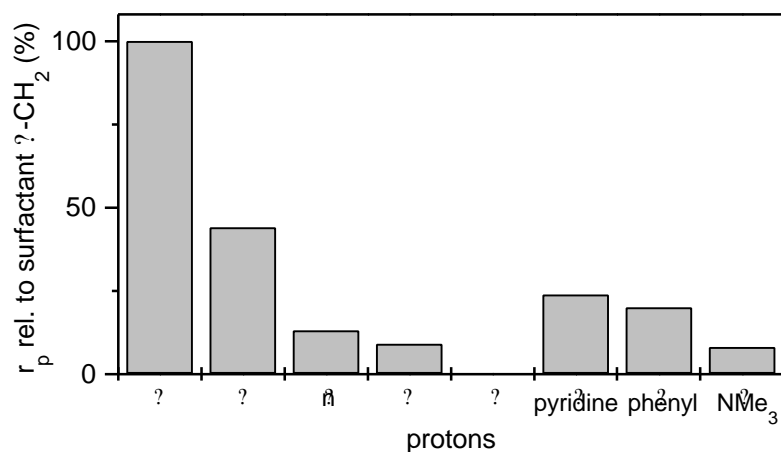


Figure 5.9. Paramagnetic ion -induced spin-lattice relaxation rates (r_p) of the protons of **5.1g** in $Zn(DS)_2$ solution and of $Zn(DS)_2$ in the presence of **5.1g**, normalised to r_p for the surfactant $-CH_2$. The solutions contained 25 mM of $Zn(DS)_2$, 8 mM of **5.1g** and 0 or 0.2 mM of $DyCl_3$.

relative to r_p for the surfactant $-$ methylene protons. In order to provide a frame of reference, also the relative paramagnetic relaxation rates of the CTAB protons are depicted. The latter show a clear decrease upon going from the headgroup towards the end of the hydrocarbon chain. The values for both dienophiles are of a magnitude somewhere between those of the 77 and the n^{77} methylene protons of CTAB. Consequently, on average they are somewhat farther away

from the paramagnetic ions than the α protons, but not as far as the β protons. Interestingly, the introduction of an ionic group (compare **5.1f** with **5.1c**) results in a modest decrease of the average distance to the paramagnetic ion. Presumably, two counteractive effects are operative. The presence of a charged group might well result in a strong shift of the average binding location towards the outer regions of the micelle, resulting in an increased influence of the paramagnetic ion on the rate of relaxation. On the other hand, the electrostatic repulsion between the charged substituent and the paramagnetic counterion will result in a decrease of the effect of this ion on the relaxation rate.

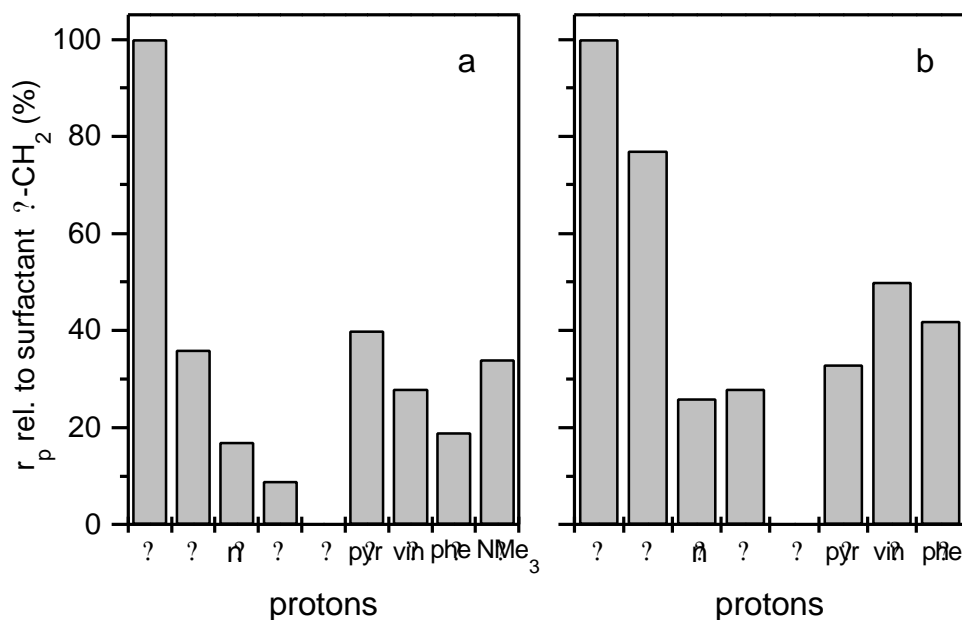


Figure 5.10. Paramagnetic ion induced spin-lattice relaxation rates (r_p) of the protons of **5.1c** (a) and **5.1g** (b) in SDS solution and of SDS in the presence of **5.1c** or **5.1g**, normalised to r_p for the surfactant α -CH₂. The solutions contained 50 mM of SDS, 8 mM of **5.1c** or **5.1g** and 0 or 0.2 mM of DyCl₃ and 0 or 0.6 mM of cyclen.

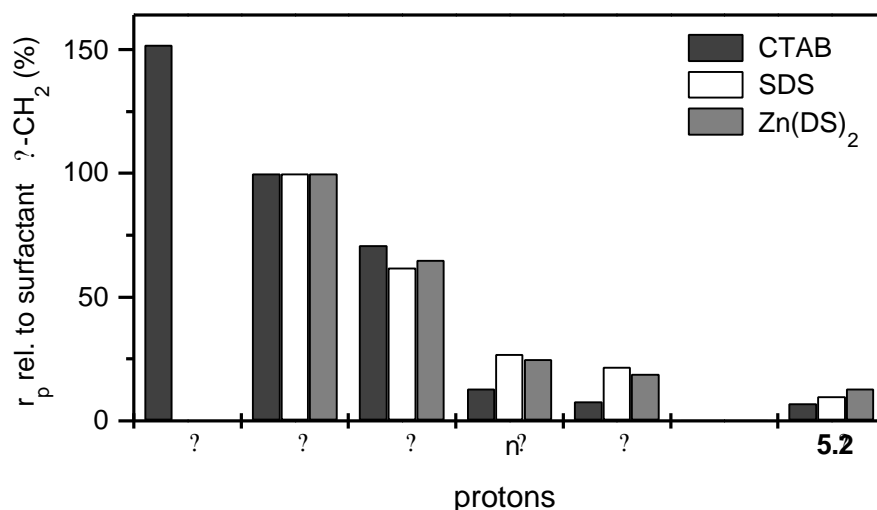


Figure 5.11. Paramagnetic ion induced spin-lattice relaxation rates (r_p) of the protons of **5.2** in CTAB, SDS or $Zn(DS)_2$ solution and of these surfactants in the presence of **5.2**, normalised to r_p for the surfactant $\text{?}-\text{CH}_2$. The solutions contained 25 mM of $Zn(DS)_2$, 50 mM of CTAB or SDS, 3 mM of **5.2** and 0 or 0.4 mM of $[Cu(EDTA)]^{2-}$ for CTAB solutions and 0 or 0.2 mM of $Cu(NO_3)_2$ for SDS and $Zn(DS)_2$ solutions.

Analogous studies on dienophiles **5.1c** and **5.1g** in SDS and $Zn(DS)_2$ lead to essentially the same conclusions. Figure 5.9 shows the relaxation data for **5.1g** in $Zn(DS)_2$ solutions. The corresponding data for **5.1c** could not be measured due to solubility problems. Analogously, Figure 5.10 shows the relaxation data of **5.1c** and **5.1g** in SDS solutions.

In conclusion, for all dienophile / surfactant combinations the average distance between the Diels-Alder reagent and the paramagnetic ion is intermediate between the corresponding distances of the ? and the n protons of the surfactant. Hence, the dienophile resides in the *outer regions* of the micelle.

The effects of paramagnetic ions on the relaxation rate of diene **5.2** in CTAB, SDS and $Zn(DS)_2$ solutions are illustrated in Figure 5.11. In this case the relative value of r_p is invariably smaller than the corresponding effect on the ?^{77} methyl protons of the surfactant. This trend clearly demonstrates that diene **5.2**, in contrast to the dienophiles, is located in the *interior* of the micelle and spends little time at the surface.

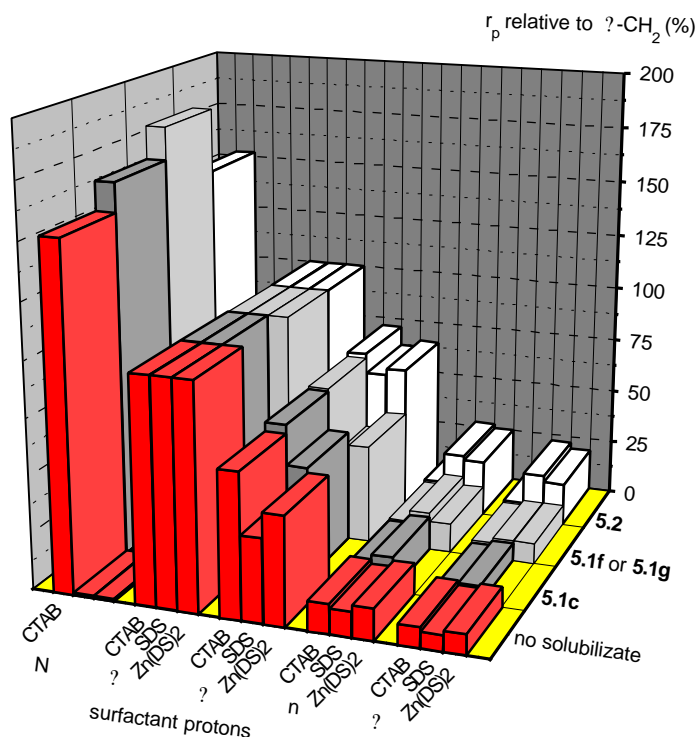


Figure 5.12. Effect of the solubilizate on the paramagnetic ion-induced spin-lattice relaxation rates (r_p) of the protons of CTAB, SDS or $Zn(DS)_2$, normalised to r_p of the surfactant $-CH_2$. The solutions contained 25 mM of $Zn(DS)_2$, 50 mM of CTAB or SDS, 3 mM of **5.2** and 8 mM of **5.1c**, **5.1f** or **5.1g** and 0 or 0.4 mM of $[Cu(EDTA)]^{2-}$ for CTAB solutions and 0 or 0.2 mM of $Cu(NO_3)_2$ for SDS and $Zn(DS)_2$ solutions.

Careful analysis of the influence of the character of the solubilizate on the relaxation data of the surfactant led to another interesting observation. Figure 5.12 summarises these data. The frontal row of bars represents the relative r_p values of the different surfactant protons in the absence of any solubilizate. The second and third row show the corresponding effects in the presence of 8 mM of **5.1c**, **5.1f** or **5.1g**. The relative paramagnetic relaxation rates are similar to those of the pure surfactant. Hence, the introduction of these compounds into a micellar solution does not lead to a significant perturbation of the alkyl chains of the micelle. Yet, when **5.2** is added to solutions of SDS and $Zn(DS)_2$, significant increases in the relative paramagnetic relaxation rates of the $?$, the n and the $?$ protons are observed. Apparently, the presence of a nonpolar solute in the interior of these micelles forces the alkyl chains of the individual surfactant molecules towards the surface. Curiously, for CTAB this effect is completely absent. This might be a result of the increased length of the alkyl chain of this surfactant compared to the two anionics, ensuring an increased tolerance towards incorporation of a solubilizate. In the literature, studies comparing the solubilisation in SDS micelles^{75c}.

In summary, the NMR studies indicate different average binding locations for diene and dienophile. The diene resides preferentially in the interior of the micelles, which is not surprising in view of its pronounced nonpolar character. The dienophiles, on the other hand, are located more towards the surface of the aggregates. This behaviour has important implications for the rationalisation of the kinetic data. Clearly, when the Diels-Alder reagents are not homogeneously distributed over the micellar pseudophase, analysis according to the pseudophase model will provide erroneous results. Using this model, a second-order rate constant in the micellar pseudophase will be obtained that is too low. However, the partition coefficients that are produced using this model are still useful, as long as one bears in mind that they represent the ratio of the *average* concentrations of solubilisate in the micellar phase and in the aqueous phase.

Another consequence of the above analysis is, that the surprising inefficiency of micellar aggregates to catalyse Diels-Alder reactions can now be rationalised. Obviously, micelles are able to bind diene and dienophile efficiently but in different parts of the micelle. The reactions seems to take place at the surface of the micelle in a rather aqueous environment, where the concentration of diene is low.

The only micellar system that shows efficient catalytic behaviour is $\text{Cu}(\text{DS})_2$. These micelles concentrate dienophile and copper ion at their surface, thereby promoting complexation of these compounds. Since $\text{Cu}(\text{DS})_2$ aggregates are also capable of binding **5.2** better than CTAB and SDS micelles, the local concentration of **5.2** at the surface of the $\text{Cu}(\text{DS})_2$ micelles is apparently high enough to allow a modest rate enhancement compared to the situation of fully complexed dienophile in pure water. Note that at concentrations slightly higher than the *cmc* of $\text{Cu}(\text{DS})_2$, very efficient coordination of the dienophile to copper can take place, which, in the absence of the surfactant, requires copper ion concentrations which are orders of magnitude higher.

In retrospect, this study has demonstrated the limitations of two commonly accepted methods of analysing solubilisation and micellar catalysis, respectively. It has become clear that solubilisate ring-current induced shifts need to be interpreted with due caution. These data indicate a proximity of solubilisate and parts of the surfactant and, strictly, do not specify the location within the micelle where the encounter takes place. Also the use of the pseudophase model for bimolecular reactions requires precaution. When distribution of the reactants over the micelle is not comparable, erroneous results are likely to be obtained.

5.3 Conclusions

The Diels-Alder reaction of dienophiles **5.1a-e**, containing neutral, cationic or anionic substituents, with diene **5.2** in the absence of Lewis acids is retarded by micelles of CTAB, SDS and C_{12}E_7 . In the situation where the dienophile does not bind to the micelle, the reaction is inhibited because uptake of

5.2 in the micelles lowers its concentration in the aqueous phase. However, retardations are most pronounced when there is essentially complete binding of the dienophile to the micelle. In this case the reaction is likely to take place at the micellar surface, where it still experiences a water-like environment. The retardation mainly results from a significant difference in the binding locations of **5.1** and **5.2**, with the dienophiles preferring the outer regions of the micelle and the diene residing in the interior. Evidence comes from solubilisate-induced aromatic shifts in the proton spectrum of the surfactants as well as from paramagnetic ion-induced relaxation rate enhancements of the $^1\text{H-NMR}$ signals of the solubilisate. The latter experiments also show that **5.2**, in contrast to **5.1**, perturbs the micelles of SDS and $\text{Cu}(\text{DS})_2$. In the situation of inhomogeneous distribution of **5.1** and **5.2** over the micelle, kinetic analysis using the pseudophase model, that has been so successful for many other bimolecular micelle-catalysed processes, will lead to erroneous estimates of the second-order rate constant in the micellar pseudophase.

In contrast to the situation in the absence of catalytically active Lewis acids, micelles of $\text{Cu}(\text{DS})_2$ induce rate enhancements up to a factor 1.8×10^6 compared to the uncatalysed reaction in acetonitrile. These enzyme-like accelerations result from a very efficient complexation of the dienophile to the catalytically active copper ions, both species being concentrated at the micellar surface. Moreover, the higher affinity of **5.2** for $\text{Cu}(\text{DS})_2$ compared to SDS and CTAB ($P_{5.2} = 96$ versus 61 and 68, respectively) will diminish the inhibitory effect due to spatial separation of **5.1** and **5.2** as observed for SDS and CTAB.

5.4 Experimental section

Materials.

Trans-chalcone (**5.4**) (mp 57.1 - 57.7 °C) was obtained from Aldrich and recrystallised from ethanol. Cyclopentadiene (**5.2**) was prepared from its dimer (Merck-Schuchardt) immediately before use. Demineralised water was distilled twice in a quartz distillation unit. $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (Merck), $\text{DyCl}_3 \cdot 6\text{H}_2\text{O}$ (Aldrich), KNO_3 (Merck), cetyl trimethylammonium bromide (CTAB, Merck), sodium dodecylsulfate (SDS, BDH Chemicals), dodecyl heptaoxyethylene ether (C_{12}E_7 , Nikko) and ethylenediaminetetraacetic acid tetrasodium salt trihydrate (EDTA, Aldrich) were of the highest purity available. 1,4,7,10-Tetraazacyclododecane (cyclen) has been kindly provided by Erik Keller. $\text{Cu}(\text{DS})_2$ and $\text{Zn}(\text{DS})_2$ have been prepared following literature procedures^{70a} and were crystallised from water. Compounds **1a-g** have been prepared by an aldol condensation of the corresponding substituted aldehyde with 2-acetylpyridine as has been described in Chapter 2. $^1\text{H-NMR}$

measurements were performed in D₂O (99.9% D, Aldrich). Stock solutions of **5.1c** and **5.4** were prepared in methanol-d₄ (99.8% D, CIL).

Endo-exo ratios.

Endo-exo ratios of the micelle-catalysed reactions have been determined by adding 0.25 mmol of **5.1c** and 0.5 mmol of **5.2** to a solution of 5 mmol of surfactant and 0.005 mmol of EDTA in 50 ml of water in carefully sealed 50 ml flasks. The solutions were stirred for 7 days at 26 °C and subsequently freeze-dried. The SDS and CTAB containing reaction mixtures were stirred with 100 ml of ether. Filtration and evaporation of the ether afforded the crude product mixtures. Extraction of the Diels-Alder adducts from the freeze-dried reaction mixture containing C₁₂E₇ was performed by stirring with 50 ml of pentane. Cooling the solution to -18 °C resulted in precipitation of the surfactant. Filtration and evaporation of the solvent afforded the adduct mixture. Endo-exo ratios were obtained from the crude product mixtures using ¹H-NMR as described in Chapter 2.

Kinetic measurements.

All kinetic measurements were performed using UV-vis spectroscopy (Perkin Elmer λ2, λ5 or λ12 photospectrometers) as described in Chapter 2.

Conductivity measurements.

Conductivity measurements were performed using a Wayne-Kerr Autobalance Universal Bridge B642 fitted with a Philips electrode PW 95121/01. The solution in the cell was stirred magnetically and thermostatted at 25 (±0.1) °C. The surfactant was added from a stock solution in water in portions of 50 μl and the conductivity was measured. *C_{mcs}* were obtained from the intersection of the tangents drawn before and after the break in the conductivity versus concentration plot. The degree of counterion binding is taken as one minus the ratio of these tangents.

NMR measurements.

Routine spectra were taken on a Varian VXR 200 MHz or Varian VXR 300 MHz spectrometer. The aromatic shift measurements and the paramagnetic relaxation measurements were performed on a Bruker AC 250 MHz spectrometer. Proton chemical shifts were determined relative to the signal of HOD (4.63 ppm). Paramagnetic relaxation times were determined using the inversion recovery experiment. The variable delay times between the 180° and the 90° pulse were chosen so that they cover the relaxation process during the time-span of minimally five times T₁. The 10-16 different delay times were in a random order so as to minimise systematic errors that might result from fluctuations of the strength of the magnetic field during the experiment. The delay time between

subsequent pulse sequences was at least five times T_1 . The T_1 values were calculated using a least squares fitting procedure available on the Bruker software.

In a typical experiment 5-10 μ l of a stock solution of the **5.1** or **5.2** in D_2O or CD_3OD was added to a 50 mM surfactant solution in D_2O , resulting in a concentration of dienophile and diene of 8.0 and 3.0 mM, respectively. After determination of the proton spin-lattice relaxation times, a stock solution of the paramagnetic species in D_2O was added and the relaxation time measurements were repeated. For CTAB solutions, $[Cu(EDTA)]^{2-}$, prepared in situ from $Cu(NO_3)_2 \cdot 3H_2O$ and 1.2 equivalent of $Na_4EDTA \cdot 3H_2O$, served as paramagnetic species in 0.4 mM concentration. For measurements on **5.2** in $Zn(DS)_2$ and SDS solutions, $Cu(NO_3)_2$ was added, resulting in a 0.2 mM concentration. For measurements on **5.1** in $Zn(DS)_2$, $DyCl_3 \cdot 6H_2O$ was added at 0.2 mM concentration. For SDS micelles, three equivalents (relative to Dy^{3+}) of cyclen was added to prevent direct interaction between Dy^{3+} and the dienophile⁸³.

Appendix 5.1

Critical micelle concentrations and counterion binding (?) of cetyltrimethylammonium bromide (CTAB), sodium dodecylsulfate (SDS) and cobalt, nickel, copper and zinc didodecylsulfate ($M(DS)_2$) in pure water and under reaction conditions, as determined by conductivity measurements at 25°C^a.

surfactant	water		under reaction conditions	
	cmc (mM)	? (%)	cmc (mM)	? (%)
CTAB	0.89 ^b	81 ^b	0.87	71
SDS	8.14 ^b	60 ^c	7.58	61
Co(DS) ₂	1.17	90	1.04	88
Ni(DS) ₂	1.19	92	1.09	90
Cu(DS) ₂	1.20	89	1.11	87
Zn(DS) ₂	1.24	86	1.10	84

^a Reaction conditions: $[5.2] = 1.0 \cdot 10^{-3}$ M; $[1\text{-propanol}] = 9.9 \cdot 10^{-2}$ M; $[5.1c] = 2.2 \cdot 10^{-5}$ M. ^b Data taken from reference 12. ^c Data taken from reference 84.

Appendix 5.2

Assuming complete binding of the dienophile to the micelle and making use of the pseudophase model, an expression can be derived relating the observed pseudo-first-order rate constant k_{obs} to the concentration of surfactant, $[S]$. Assuming a negligible contribution of the reaction in the aqueous phase to the overall rate, the second-order rate constant in the micellar pseudophase k_m is given by:

$$(A2.1)$$

$$k_m = \frac{k_{obs}}{[5.2]_m}$$

Next, $[5.2]_m$ can be expressed as a function of the partition coefficient $P_{5.2}$ and the concentration of surfactant in the equations:

$$P_{5.2} = \frac{[5.2]_m}{[5.2]_w} \quad (2.2)$$

$$[5.2]_w = \frac{n_{5.2,w}}{V_w} = \frac{n_{5.2,t} + n_{5.2,m}}{V_w} = \frac{n_{5.2,t} + [5.2]_m V_m}{V_w} \quad (A2.3)$$

Where $n_{5.2,w}$, $n_{5.2,m}$ and $n_{5.2,t}$ are, respectively, the number of moles of **5.2** in the aqueous phase, the micellar phase and the total of the two. V_w and V_m are the volumes of the aqueous phase and the micellar pseudophase.

Substitution of A2.2 in A2.3 and solving for $1/[5.2]_m$ gives:

$$\frac{1}{[5.2]_m} = \frac{V_w}{P_{5.2} n_{5.2,t}} + \frac{V_m}{n_{5.2,t}} \quad (A2.4)$$

The volume of the micellar pseudophase can be estimated from the molar volume of the micellised surfactant $V_{mol,S}$:

$$V_m = ([S] - cmc) V_t V_{mol,S} \quad (A2.5)$$

Substituting A2.5 in A2.4 and substituting $n_{5.2,t}$ with $[5.2]_t V_t$ yields:

$$\frac{1}{[5.2]_m} = \frac{V_w}{P_{5.2} [5.2]_t V_t} + \frac{([S] - cmc) V_{mol,S}}{[5.2]_t V_t} \quad (A2.6)$$

Combining A2.6 and A2.1 gives the final equation from which k_m and $P_{5.2}$ can be obtained by plotting $1/k_{app}$ versus $[S]$.

$$\frac{1}{k_{app}} = \frac{[5.2]_t}{k_{obs}} + \frac{V_{mol,S}}{k_m} [S] + \frac{V_w}{P_{5.2} V_t k_m} + \frac{cmc V_{mol,S}}{k_m} \quad (A2.7)$$

Appendix 5.3

When the dienophile does not bind to the micelle, reaction will take place exclusively in the aqueous phase so that the second-order rate constant of the reaction in this phase (k_w) is directly related to the ratio of the observed pseudo-first-order rate constant and the concentration of diene that is left in this phase.

$$k_w = \frac{k_{obs}}{[5.2]_w} \quad (A3.1)$$

The partition coefficient of **5.2** ($P_{5.2}$) can be expressed in terms of the concentration of **5.2** in the aqueous phase ($[5.2]_w$), the total number of moles of **5.2** in the reaction mixture ($n_{5.2,t} = n_{5.2,w} + n_{5.2,m}$), as well as the volumes of the aqueous phase (V_w) and the micellar phase (V_m).

$$P_{5.2} = \frac{[5.2]_m}{[5.2]_w} = \frac{1}{[5.2]_w} \frac{n_{5.2,t}}{V_m} = \frac{[5.2]_w V_w}{V_m} \frac{1}{[5.2]_w} \frac{n_{5.2,t}}{V_m} = \frac{V_w}{V_m} \frac{n_{5.2,t}}{[5.2]_w V_w} \quad (A3.2)$$

Rewriting and substitution of A2.5 and substitution of $n_{5.2,t}$ with $[5.2]_t V_t$ gives:

$$\frac{1}{[5.2]_w} = \frac{P_{5.2} V_{mol,S}}{[5.2]_t} [S] - \frac{P_{5.2} cmc V_{mol,S}}{[5.2]_t} = \frac{V_w}{[5.2]_t V_t} \quad (A3.3)$$

Combining A3.1 and A3.3 and rewriting results in:

$$\frac{1}{k_{app}} = \frac{[5.2]_t}{k_{obs}} = \frac{P_{5.2} V_{mol,S}}{k_w} [S] - \frac{P_{5.2} cmc V_{mol,S}}{k_w} = \frac{V_w}{k_w V_t} \quad (A3.4)$$

Using Equation A3.4, the partition coefficient of **5.2** can be obtained from the slope of the plot of the apparent second-order rate constant versus the concentration of surfactant and the independently determined value of k_w .

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Epilogue

In the final chapter of this thesis, the work described in the preceding chapters is evaluated. Furthermore, two pivotal themes of this work, Lewis acid - Lewis base interactions in water and hydrophobic effects, are reviewed. Finally, the prospects of Lewis-acid catalysis in aqueous solution are discussed.

6.1 Introduction

Now that all the experimental work has been presented in the preceding chapters, the opportunity arises to survey what has been accomplished. In the next section we will evaluate whether or not the goals as formulated at the end of Chapter 1 have been reached.

During the work described in this thesis, we were confronted with two topics that warrant general comments. The first involves the interaction between Lewis acids and Lewis bases in aqueous solution. Although enthusiasm for use of water as a medium for Lewis-acid catalysed reactions is rising rapidly, it is appropriate to address some of the problems that are too often overlooked, but are likely to be encountered using this very special solvent. Section 6.3 elaborates on these problems

The second topic concerns hydrophobic effects. When working with relatively apolar compounds in water, as we did in this study, hydrophobic effects are ubiquitous. A deeper understanding of these effects would be of great help in recognising and employing them in organic chemistry. Fortunately, after decades of extensive discussions, it seems as if a consistent molecular picture is now emerging, which will be outlined in Section 6.4.

Finally, Section 6.5 will close this thesis by suggesting lines for continuation of the research.

6.2 Goals and achievements

At the outset of the work described in this thesis we formulated a number of questions.

First of all, given the well recognised promoting effects of Lewis-acids and of aqueous solvents on Diels-Alder reactions, we wanted to know if these two effects could be combined. If this would be possible, dramatic improvements of rate and endo-exo selectivity were envisaged.

Studies on the Diels-Alder reaction of a dienophile, specifically designed for this purpose are described in Chapter 2. It is demonstrated that Lewis-acid catalysis in an aqueous medium is indeed feasible and, as anticipated, can result in impressive enhancements of both rate and endo-exo selectivity. However, the influences of the Lewis-acid catalyst and the aqueous medium are not fully additive. It seems as if water diminishes the catalytic potential of Lewis acids just as coordination of a Lewis acid diminishes the beneficial effects of water. Still, overall, the rate of the catalysed reaction

in water is faster than in most organic solvents, justifying further development of Lewis-acid catalysis of Diels-Alder reactions in water.

A second question involves the influence of ligands on the rate and selectivity of the Lewis-acid catalysed Diels-Alder reaction in water. In Chapter 3 we have demonstrated that nearly all the ligands studied induce a significant decrease in the affinity of the catalyst for the dienophile. This effect is accompanied by a modest reduction of the rate of the Diels-Alder reaction of the ternary dienophile - catalyst - ligand complex.

Most significantly, one class of ligands, the aromatic α -amino acids, shows deviating behaviour due to a specific ligand - dienophile interaction. This interaction can be employed successfully in enantioselective catalysis, allowing, for the first time, the effect of aqueous solvents on the enantioselectivity of a chiral Lewis-acid catalysed reaction to be studied. It turned out that water is capable of inducing a significant increase in the enantioselectivity as compared to organic solvents.

Of all the work described in this thesis, this discovery is probably the most significant. Given the fact that the arene - arene interactions underlying the observed enantioselectivity of the Diels-Alder reactions described in Chapter 3 are also encountered in other organic reactions, we infer that, in the near future, the beneficial influence of water on enantioselectivity can also be extended to these transformations. Moreover, the fact that water can now be used as a solvent for enantioselective Lewis-acid catalysed reactions facilitates mechanistic studies of these processes, because the number of equilibria that need to be considered is reduced. Furthermore, knowledge and techniques from aqueous coordination chemistry can now be used directly in enantioselective catalysis.

Having observed the beneficial effects of water on the rate and enantioselectivity of one particular Diels-Alder reaction, an answer to the third question, addressing the scope of Lewis-acid catalysis of Diels-Alder reactions in water, became all the more desirable. Chapter 4 describes an investigation of the limitations of this process. It is concluded that in water efficient catalysis is feasible only for Diels-Alder reactants capable of bi- or multidentate binding to the catalyst. Unfortunately, hardly any common diene or dienophile fulfils this requirement. In an attempt to extend the scope of Lewis-acid catalysis in water we made use of a strongly chelating diamine as a coordinating auxiliary, introduced via a Mannich reaction. This approach may well be expected to subject those dienes or dienophiles capable of undergoing a Mannich reaction with 2-(methylaminomethyl)pyridine to Lewis-acid catalysis in water. However, enantioselective Lewis-acid catalysis employing the copper - aromatic α -amino acid complexes introduced in Chapter 3 is unlikely to be successful for these compounds. The Mannich adducts coordinate in a tridentate fashion. In this arrangement a geometry resembling that shown in Scheme 3.10 is unlikely. In conclusion, at this moment the scope of Lewis-acid catalysis in aqueous solution is still rather limited.

Finally, in Chapter 5, micellar catalysis of Diels-Alder reactions is discussed. In view of the nonpolar nature of most Diels-Alder reactants, efficient micellar catalysis of this reaction was anticipated. However, this has not been observed. The results for the Diels-Alder reaction between cyclopentadiene and substituted 3-phenyl-1-(2-pyridyl)-2-propene-1-one dienophiles, discussed in

Chapter 5, may provide a rationale. Conclusions derived from a number of $^1\text{H-NMR}$ measurements indicate that cyclopentadiene has a high affinity for the interior of the micelles that were investigated, whereas the dienophile prefers the outer regions. In view of the structures of most dienes and dienophiles such a spatial separation can be expected for the majority of Diels-Alder reactions. This arrangement accounts for the unexpectedly small influence of micelles on the rates of Diels-Alder reactions as reported in the literature.

Chapter 5 also demonstrates that a combination of Lewis-acid catalysis and micellar catalysis can lead to accelerations of enzyme-like magnitudes. Most likely, these accelerations are a consequence of an efficient interaction between the Lewis-acid catalyst and the dienophile, both of which have a high affinity for the Stern region of the micelle. Hence, hydrophobic interactions and Lewis-acid catalysis act cooperatively. Unfortunately, the strength of the hydrophobic interaction, as offered by the $\text{Cu}(\text{DS})_2$ micellar system, was not sufficient for extension of Lewis-acid catalysis to monodentate dienophiles.

In summary, the work in this thesis provides an overview of what can be achieved with Lewis-acid and micellar catalysis for Diels-Alder reactions in water as exemplified by the reaction of 3-phenyl-1-(2-pyridyl)-2-propene-1-ones with cyclopentadiene. Extension of the observed beneficial effect of water on rates and particularly enantioselectivities to other systems is envisaged.

6.3 Lewis acid - Lewis base interactions in water. Implications for catalysis

This thesis has been completely devoted to catalysis by relatively hard catalysts. When aiming at the catalysis of Diels-Alder reactions, soft catalysts are not an option. Soft catalysts tend to coordinate directly to the carbon - carbon double bonds of diene and dienophile, leading to an activation towards nucleophilic attack rather than to a Diels-Alder reaction¹. This is unfortunate, since in water, catalysis by hard catalysts suffers from a number of intrinsic disadvantages, which are absent for soft catalysts.

6.3.1 Hard Lewis acids and bases

Water molecules unite in them hard, strongly Lewis-basic, as well as hard, strongly Lewis-acidic sites. In the solid and the liquid state of water, interactions between these sites result in the formation of a hydrogen-bond network, to which water owes its unique properties. Solutes that are capable of interacting efficiently with these hard sites, generally exhibit a high solubility in water. This conclusion applies in particular to salts containing hard ions. Water is one of the most efficient solvents in weakening the interaction between hard positive and hard negative charges.

Analogously, water is extremely efficient in weakening hard Lewis acid - hard Lewis base interactions. Consequently, when aiming at catalysis by hard Lewis acids, the inefficiency of the interaction between the catalyst and the substrate is a serious problem. Strangely enough, this characteristic of water is not recognised by many researchers working with hard Lewis acids in

aqueous solutions. Particularly the use of the extremely hard trivalent lanthanide cations has recently received considerable attention in synthetic organic chemistry (see Section 2.1.1). In aqueous solution, these ions are observed to induce an increase in yields and selectivities of a large number of organic reactions, from which it is concluded that Lewis-acid catalysis is operative. Unfortunately, for the majority of these reactions, no direct evidence of an interaction between catalyst and substrate is provided. Regarding the structure of most of the employed reactants, such an interaction is expected to be extremely weak, if present at all. Note that even the bidentate 3-phenyl-1-(2-pyridyl)-2-propene-1-one dienophiles employed in this thesis have a negligible tendency to interact with lanthanide ions in aqueous solution. Hence, the term “Lewis-acid catalysis” might well be ill-chosen for many of these reactions. Most likely, the beneficial effects of the Lewis-acidic ions on these processes is indirect. In many of the reactions that have been reported to benefit from Lewis-acids in aqueous media, such as the aldol reaction, the Michael addition and the Mannich reaction, proton-transfer steps are involved. It might well be that mainly these steps are affected by the presence of Lewis-acid catalysts in water. Note also that aqueous solutions of salts of multivalent cations contain a significant amount of metal-ion coordinated hydroxide ions together with a similar amount of H_3O^+ . In other words, Lewis acids enhance the dissociation of water. Reactions involving proton transfer steps are likely to be influenced in such media.

Turning the argument around: reactions that do *not* involve proton transfer steps will only experience a significant effect of the Lewis acids if a direct interaction exists between catalyst and reactant. The conventional Diels-Alder reaction is a representative of this class of reactions. As long as monodentate reactants are used, the effects of Lewis acids on this reaction do not exceed the magnitude expected for simple salt effects, i.e. there are no indications for a direct interaction between Lewis-acid and substrate.

We conclude that, when employing hard Lewis-acids in aqueous solution, the term “Lewis-acid catalysis” should be used with caution, and only after evidence for a direct interaction between Lewis-acid and substrate has been obtained.

However, once coordination of the substrate to the Lewis-acid catalyst has been achieved, the use of aqueous media can have marked benefits over organic solvents. For instance, separation of product and catalyst is usually facilitated. Significantly, the fact that water is so efficient in breaking interactions between Lewis acids and Lewis bases (and also electrostatic interactions) turns into a considerable benefit. In organic solvents, enhanced interaction of catalytically active ions with counterions tends to hamper the interaction with the substrate. In water, these ion pairing effects are largely absent. Clustering of the catalytic species is another complication that can be encountered in organic solvents, but is infrequent in water. Consequently, mechanistic investigations of catalytic processes tend to be less complicated in water than in organic solvents.

6.3.2 *Soft Lewis acids and bases*

In contrast to the extreme efficiency with which water breaks up interactions between hard Lewis

acids and hard Lewis bases, it has only little influence on the interactions between soft Lewis acids and soft Lewis bases. Small and poorly polarisable water molecules are not able to interact strongly with large polarisable entities. Consequently, reactions in which catalysis proceeds through interaction of the catalyst with apolar but polarisable parts of organic molecules, such as carbon-carbon double bonds, need not fear interference of water. Hence, reactions like hydrogenations and hydroformylations, catalysed by soft catalyst containing palladium, rhodium or ruthenium centres, can be successfully performed in aqueous solution. However, the absence of efficient interactions between water and the catalyst gives rise to problems with regard to the solubility of the catalyst. As a result, many of the ligands that are employed in these processes need to be equipped with highly polar or ionic groups to ensure water solubility.

6.4 Hydrophobic effects. Implications for organic reactivity in water

Throughout this thesis reference has been made to hydrophobic effects. Enforced hydrophobic interactions are an important contributor to the acceleration of uncatalysed and also of the Lewis-acid catalysed Diels-Alder reactions which are described in this thesis. Moreover, they are likely to be involved in the beneficial effect of water on the enantioselectivity of the Lewis-acid catalysed Diels-Alder reaction, as described in Chapter 3. Because arguments related to hydrophobic effects are spread over nearly all chapters, and ideas have developed simultaneously, we summarise our insights at the end of this thesis.

Through the years, the molecular picture behind hydrophobic effects has been hidden under a cloak of misunderstandings which are for a large part of semantic origin. The effects are real, but have been given names that have contributed little to our understanding. Extremely misleading is the term “hydrophobic”, suggesting a phobia for water experienced by the solute. However, from the perspective of the solute, there is no phobia for water, in the sense that the interactions of the solute with the surrounding water molecules are comparable to- and sometimes even stronger than the interaction of the same solute molecule with its neighbours in the pure liquid state². Hence, if it would be up to the solute to decide whether to interact with a neighbouring solute molecule in aqueous solution, or stay within its own hydration shell, it would choose the latter. Nevertheless, there exists a tendency for nonpolar molecules to stick together in aqueous solution (hydrophobic interaction). This cannot be a result of the interactions between the nonpolar molecules, but is imposed upon the solutes by water. It is the strong interaction between the water molecules that causes the low solubility of nonpolar compounds in water and squeezes the nonpolar molecules together.

A second important contributor to the misunderstanding of hydrophobic effects is the term “iceberg”, which is used in the discussion on the hydration of apolar molecules or groups. There exist strong indications for structuring of the water molecules in the direct vicinity of nonpolar solutes, but these water molecules are by no means frozen or more ice-like than bulk water. There are no experimental indications for a significant increase in the number or strength of the hydrogen bonds in the

hydrophobic hydration shell. However, there are strong indications for a reduced entropy of the water molecules that make up these shells as compared to bulk water. Hence, structuring of hydration shell water exists, but only in an *entropic* sense.

In the hope of having done away with these misunderstandings, we now address the molecular origin of the hydrophobic hydration as well as the hydrophobic interaction. Note that comprehension of hydrophobic hydration is a prerequisite for understanding hydrophobic interactions, since hydrophobic interactions always involve a (partial) reversal of the hydrophobic hydration.

6.4.1 Hydrophobic hydration

If one would ask a chemist not burdened with any knowledge about the peculiar thermodynamics that characterise hydrophobic hydration, what would happen upon transfer of a nonpolar molecule from the gas phase to water, he or she would probably predict that this process is entropy driven and enthalpically highly unfavourable. This opinion, he or she would support with the suggestion that in order to create room for the nonpolar solute in the aqueous solution, hydrogen bonds between water molecules would have to be sacrificed.

The real situation is that, at ambient temperature, transfer of an ordinary nonpolar solute from the gas phase to water is characterised by a large reduction of the entropy and is enthalpically favourable. Apparently, water is capable of preventing the breaking of hydrogen bonds, but not without paying a price in the form of a reduction of the entropy. There are strong indications that this reduction in entropy can be attributed to the orientational constraints imposed upon the water molecules entangled in the hydrophobic hydration shells³. The number of orientations that these molecules can adopt while maintaining their hydrogen bonds with the surrounding water molecules is significantly reduced by the presence of the solute. Since the nonpolar solute cannot accept hydrogen bonds, keeping the fully hydrogen-bonded state is likely to lead to the observed orientation with one O-H bond parallel to the surface of the solute. Apparently, this arrangement in a hydrophobic hydration shell is favoured over the situation in which hydrogen bonds are broken.

However, if the formation of the hydrophobic hydration shell is hindered, the system prefers the sacrifice of hydrogen bonds. For instance, upon increasing the temperature, water tends towards the breaking of hydrogen bonds, as reflected by an increase of the enthalpy of hydration of nonpolar compounds with a concomitant less reduced hydration entropy. At higher temperatures, breaking of hydrogen bonds requires less additional energy, whereas the construction of an relatively ordered hydrophobic hydration shell becomes increasingly difficult with increasing disorder in bulk water.

Similar effects are observed upon addition of cosolutes, such as salts and alcohols. The formation of hydrophobic hydration shells becomes increasingly unfavourable with increasing cosolute concentration. Apparently, the structural requirements of the hydrophobic hydration shell do not tolerate the presence of significant concentrations of foreign species in the aqueous solution.

Finally, also size and shape of the nonpolar solute seem to influence the formation of hydrophobic hydration shells. Particularly the curvature of the nonpolar surface has been suggested to be

important⁴. Small spherical particles allow the formation of a hydrophobic hydration shell, without a significant sacrifice of hydrogen bonds. As the curvature of the nonpolar surface decreases, the extent of breaking of hydrogen bonds increases. Hydration of a flat surface is characterised by a significant number of dangling hydrogen bonds⁵. In the extreme of a nonpolar cavity, it is evident that upon entering, the water molecules sacrifice hydrogen bonds. Hence, hydration of these cavities will be characterised by a unfavourable enthalpy change⁶.

Although temperature, cosolutes and curvature have dramatic effects on the entropy and enthalpy of hydration of nonpolar solutes, these effects largely compensate each other, so that the Gibbs energy is much less affected. Hence, the Gibbs energy of the state in which a hydrophobic hydration shell is formed is only slightly lower than that of the situation where hydrogen bonds are sacrificed instead.

6.4.2 Hydrophobic interactions

Interactions between nonpolar compounds are generally stronger in water than in organic solvents. At concentrations where no aggregation or phase separation takes place, *pairwise hydrophobic interactions* can occur. Under these conditions, the lowest energy state for a solute molecule is the one in which it is completely surrounded by water molecules. However, occasionally, it will also meet other solute molecules, and form short-lived encounter complexes. In water, the lifetime of these complexes exceeds that in organic solvents, since the partial desolvation that accompanies the formation of these complexes is less unfavourable in water than in organic solvents.

Pairwise hydrophobic interactions can be used to alter the reactivity of organic molecules in water. For instance, the rate of hydrolysis reactions may be influenced significantly by the presence of hydrophobic cosolutes⁷. The effect on reactivity has been analysed by comparing the interactions between initial state and cosolute with those between transition state and cosolute⁷.

When the concentration of the nonpolar solute is increased, the entropy of mixing of the newly added molecules that drives the dissolution process, gradually diminishes. At a certain critical concentration, the entropy of mixing is insufficient to overcome the unfavourable Gibbs energy of hydration. At this concentration, phase separation will set in. Depending on the molecular structure of the solute, this process can result in the formation of a two-phase system, or the formation of an aggregated pseudophase. In water, the interactions that drive phase separation are referred to as *bulk hydrophobic interactions*. Also these interactions can be used to influence organic reactivity as exemplified by catalytic effects of aggregates. These aggregates affect the rate of organic reactions by providing a reaction medium different from that of bulk water. For monomolecular reactions this medium effect can be large. However, for bimolecular reactions the effect on the intrinsic reactivity is usually modest. Nevertheless, the effects of aggregates on the rates of bimolecular reactions can be large when the reactants are gathered in or around the aggregates. Note that also the binding of nonpolar compounds to aggregates is governed by hydrophobic interactions. In this case the hydrophobic interactions are associated with a partitioning between two (pseudo)phases, and as such, cannot be ranked under pairwise (binding to the aggregates is not transient) or bulk (as long as the

solute concentration is lower than the solubility limit) hydrophobic interactions.

A third kind of hydrophobic interaction occurs when a chemical reaction happens to force two nonpolar molecules together. *Enforced hydrophobic interactions* ensure that the rate of these reactions in water is increased as compared to organic solvents. Note that in a chemical reaction, the entropic price for the association of two hydrophobic compounds is part of the activation process. For irreversible reactions the association is permanent, which distinguishes enforced hydrophobic interactions from pairwise hydrophobic interactions. The aqueous Diels-Alder reaction is one of the most well-documented examples in which enforced hydrophobic interactions are operative. For this transformation, strong indications exist that the reaction centre entirely *loses* its nonpolar character in the activation process^{7a,8}. In terms of transition state theory, the initial state of the reaction in water is destabilised relative to that in organic solvents. In the transition state this effect is largely absent, so that the activation energy of the Diels-Alder reaction in water is reduced as compared to organic solvents.

The observation that in the activated complex the reaction centre has lost its hydrophobic character, can have important consequences. The retro Diels-Alder reaction, for instance, will also benefit from the breakdown of the hydrophobic hydration shell during the activation process. The initial state of this reaction has a nonpolar character. Due to the principle of microscopic reversibility, the activated complex of the retro Diels-Alder reaction is identical to that of the bimolecular Diels-Alder reaction which means this complex has a negligible nonpolar character near the reaction centre. Consequently, also in the activation process of the retro Diels-Alder reaction a significant breakdown of hydrophobic hydration takes place⁹. Note that for this process the volume of activation is small, which implies that the number of water molecules involved in hydration of the reacting system does not change significantly in the activation process.

We conclude that the beneficial effects of water are not necessarily limited to reactions that are characterised by a negative volume of activation. We infer that, apart from the retro Diels-Alder reaction also other reactions, in which no significant reduction or perhaps even an increase of solvent accessible surface area takes place, can be accelerated by water. A reduction of the nonpolar nature during the activation process is a prerequisite in these cases.

In the case of the retro Diels-Alder reaction, the nature of the activated complex plays a key role. In the activation process of this transformation, the reaction centre undergoes changes, mainly in the electron distributions, that cause a lowering of the chemical potential of the surrounding water molecules. Most likely, the latter is a consequence of an increased interaction between the reaction centre and the water molecules. Since the enforced hydrophobic effect is entropic in origin, this implies that the orientational constraints of the water molecules in the hydrophobic hydration shell are relieved in the activation process. Hence, it almost seems as if in the activated complex, the hydrocarbon part of the reaction centre is involved in hydrogen bonding interactions. Note that the transition state of a Diels-Alder reaction resembles an aromatic system¹⁰ and that there is evidence for hydrogen bond formation to aromatic systems¹¹. If this is true, this would shed a whole new light on

the way in which water can affect rates of organic reactions. Detailed studies to verify this intriguing suggestion are urgently required.

Also the arene-arene interactions, as encountered in Chapter 3, are partly due to hydrophobic effects, which can be ranked among enforced hydrophobic interactions. Simultaneous coordination of an aromatic α -amino acid ligand and the dienophile to the central copper(II) ion offers the possibility of a reduction of the number of water molecules involved in hydrophobic hydration, leading to a strengthening of the arene-arene interaction. Hence, hydrophobic effects can have a beneficial influence on the enantioselectivity of organic reactions. This effect is anticipated to extend well beyond the Diels-Alder reaction.

6.5 Prospects and incentives to future research

As a result of the growing need for clean chemistry, the use of catalytic processes is becoming increasingly popular and alternatives for organic solvents are being sought. Consequently, Lewis-acid catalysis in water is expected to be a field of considerable interest in the near future. Clearly, catalysis by soft Lewis acids in water is generally easier than catalysis by hard catalysts. In the slip stream of the success of the Ruhr Chemie Rhone-Poulenc process, more breakthroughs in the former field can be expected in the coming years, whereas catalysis by hard Lewis acids in aqueous media will remain troublesome for the time being. The use of substrates with non-chelating functionalities in reactions catalysed by hard Lewis acids is a big challenge for the future. Perhaps the use of binuclear catalysts can break the deadlock¹². The occurrence of a *reverse chelate effect* has been reported for these systems, which can lead to more pronounced selectivities in binding of monodentate compounds¹³.

It might also be possible to employ the hydrophobic effect for selective binding of a reactant to the catalyst. Interestingly, Menger et al.¹⁴ have recently used combinatorially developed catalysts for reductions and hydrolysis reactions. For the reduction of ketones in aqueous solution, the most active catalyst libraries were those that contained both hydrophobic constituents, as well as moieties exhibiting a large affinity for catalytically active metal ions^{14b}. In this thesis another example of the beneficial influence of hydrophobic effects on catalyst - substrate binding is encountered in the form of micelles, containing catalytically active counterions.

Finally, if there could be a way in which in water selective η^2 π -coordination to the carbonyl group of an α,β -unsaturated ketone can be achieved, this would be a breakthrough, since it would subject monodentate reactants to catalysis by hard Lewis acids¹⁵.

Developments along these three lines can be expected to greatly extend the yet limited utility of catalysis by hard Lewis acids in aqueous media. The work described in this thesis has demonstrated that these efforts can be rewarded by increased rate and most importantly, enantioselectivity.

We would like to conclude this thesis with the expression of the hope that in its course, we have taken away

some of the “hydrophobia” that stills exists among organic chemists, although we admit that we might have replaced it with more rational arguments. Nevertheless, the treasure can make it worthwhile to slay the dragon.

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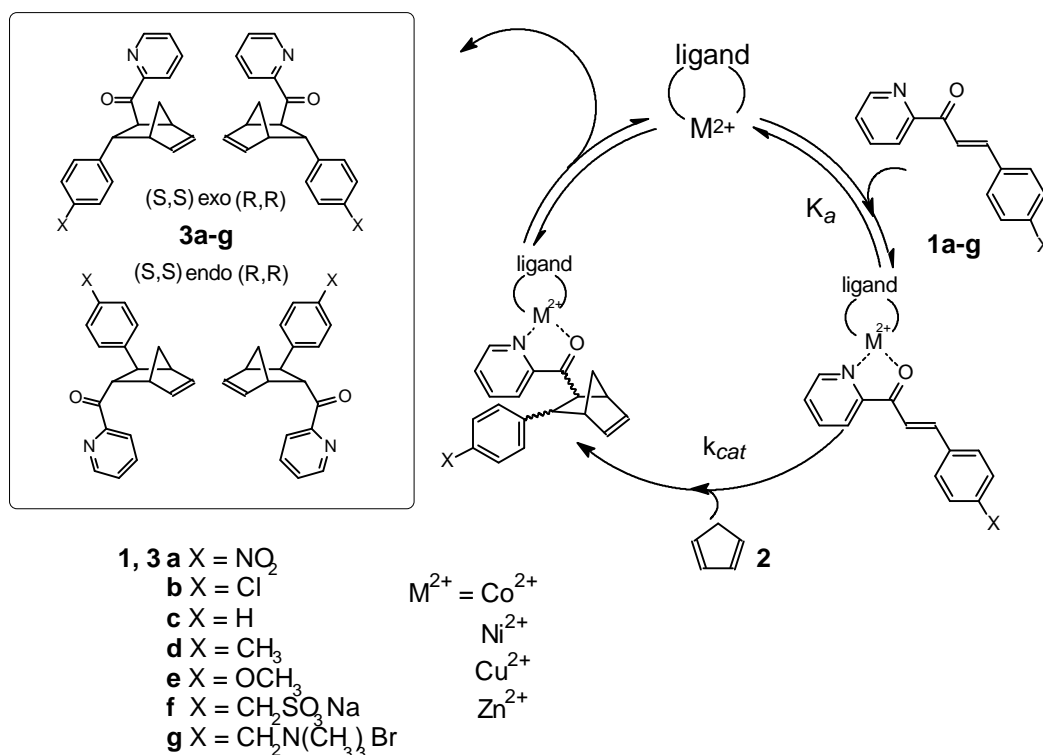
Catalysis of Diels-Alder Reactions in Water

This thesis describes a study of catalysis of Diels-Alder reactions in water. No studies in this field had been reported at the start of the research, despite the well known beneficial effects of aqueous solvents as well as of Lewis-acid catalysts on rate and endo-exo selectivity of Diels-Alder reactions in organic solvents. We envisaged that a combination of these two effects might well result in extremely large rate enhancements and improvements of the endo-exo selectivity.

In Chapter 1 mechanistic aspects of the Diels-Alder reaction are discussed. The literature on the effects of solvents and Lewis-acid catalysts on this reaction is surveyed. The special properties of water are reviewed and the effects of water on the Diels-Alder reaction is discussed. Finally, the effect of water on Lewis acid - Lewis base interactions is described.

Chapter 2 describes the results of the first detailed study of Lewis-acid catalysis of a Diels-Alder reaction in water. Substituted 3-phenyl-1-(2-pyridyl)-2-propen-1-one dienophiles (**1a-g** in Scheme 1) were found to coordinate to Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} ions in aqueous solution. This process forms the first step in the catalytic cycle shown in Scheme 1. The trend in the *equilibrium constants* for binding of **1** to these ions follows the empirical Irving-Williams series: $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} \gg \text{Zn}^{2+}$.

Upon binding to these Lewis acids, the dienophile is activated towards Diels-Alder reactions with



Scheme 1

cyclopentadiene (**2**) yielding products **3** as a mixture of racemic endo and exo adducts. The effect of Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} ions on the *second-order rate constants* for the Diels-Alder reaction of **1** with **2** follows the Irving-Williams order.

The rate of the Lewis-acid catalysed Diels-Alder reaction in water has been compared to that in other solvents. The results demonstrate that the expected beneficial effect of water on the Lewis-acid catalysed reaction is indeed present. However, the water-induced acceleration of the Lewis-acid catalysed reaction is not as pronounced as the corresponding effect on the uncatalysed reaction. The two effects that underlie the beneficial influence of water on the uncatalysed Diels-Alder reaction, enforced hydrophobic interactions and enhanced hydrogen bonding of water to the carbonyl moiety of **1** in the activated complex, are likely to be diminished in the Lewis-acid catalysed process. Upon coordination of the Lewis-acid catalyst to the carbonyl group of the dienophile, the catalyst takes over from the hydrogen bonds an important part of the activating influence. Also the influence of enforced hydrophobic interactions is expected to be significantly reduced in the Lewis-acid catalysed Diels-Alder reaction. Obviously, the presence of the hydrophilic Lewis-acid diminished the nonpolar character of **1** in the initial state.

As expected, the solvent has a significant effect on the *endo-exo selectivity* of the uncatalysed Diels-Alder reaction between **1** and **2**. In contrast, the corresponding effect on the Lewis-acid catalysed reaction is small. There is no beneficial effect of water on the endo-exo selectivity of the catalysed Diels-Alder reaction. The endo-exo selectivity in water is somewhat diminished relative to that in ethanol and acetonitrile.

We have also analysed the *effect of substituents* in the dienophile on: (1) the coordination behaviour to Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} ions, (2) the rate constants of the Diels-Alder reaction with **2**, catalysed by these ions and (3) the endo-exo selectivity of these reactions. The equilibrium constants for binding of **1** to Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} increase with increasing electron donating character of the substituents, resulting in linear Hammett plots. Hence, as expected, the equilibrium constants for binding to the Lewis-acid increase with increasing Lewis-basicity of the dienophile. The Hammett ρ -values for the different metal ions follow the Irving-William series. Satisfactory Hammett plots were obtained also for the second-order rate constants of the catalysed reaction. As expected for a normal electron demand Diels-Alder reaction, these rate constants increase with increasing electron withdrawing character of the substituents. The magnitudes of the ρ -values for the catalysed Diels-Alder reaction (0.72-0.94) are similar to those generally obtained for uncatalysed Diels-Alder reactions. This implies that the change in charge separation during the activation process of the catalysed reaction is comparable to that of the uncatalysed reaction. We conclude that the Lewis-acid catalysed Diels-Alder reaction between **1** and **2** is a concerted process. Finally, investigation of the Lewis-acid catalysed Diels-Alder reaction between **1a-e** and **2** revealed that, as long as the reaction mixture is homogeneous, substituents do not affect the endo-exo selectivity significantly.

The solvent effect on the rate constants of the Diels-Alder reaction of the ionic dienophiles **1f** and **1g**

with **2** has been studied. Interestingly, the beneficial influence of water on the rate of these reactions was comparable to that observed for the nonionic dienophiles. Apparently, a hydrophilic substituent remote from the reaction centre does not hamper the acceleration by water.

Chapter 3 describes an investigation into the effects of ligands on a Lewis-acid catalysed Diels-Alder in water. In the literature there are only a limited number of examples of systematic studies of ligand effects on Lewis-acid catalysed reactions in water. These studies mainly focus on the metal-ion catalysed decarboxylation of oxaloacetate. This reaction was observed to benefit from the presence of aromatic diamine ligands. This inspired us to investigate the influence of this class of ligands on the rate and endo-exo selectivity of the Lewis-acid catalysed Diels-Alder of **1** with **2**. We have selected 2,2'-bipyridine and 1,10-phenanthroline as target ligands and have included ethylenediamine, dimethylethylenediamine and 2-(aminomethyl)pyridine for comparison purposes. Unfortunately, none of these ligands was capable of inducing a significant increase in the equilibrium constant (K_a) for binding of **1c** to the $\text{Ni}^{2+}(\text{ligand})$ and $\text{Cu}^{2+}(\text{ligand})$ complexes. Upon addition of most ligands, the equilibrium constant K_a was reduced as compared to the value for the metal aquo ion, as expected on the basis of statistics. For most of the investigated diamine ligands, the rate constant (k_{cat}) for the Diels-Alder reaction of the ternary ligand-metal ion-dienophile complex with **2** is comparable to k_{cat} for the metal aquo ion. Deviations from this behaviour were observed only for $\text{Cu}^{2+}(2,2'\text{-bipyridine})$ and $\text{Cu}^{2+}(1,10\text{-phenanthroline})$ complexes. When compared to the copper(II) aquo ion these complexes exhibit a detrimental effect on both k_{cat} and K_a , which is most likely a result of a steric interaction between the α -hydrogens of the pyridine rings of the ligand with the α -hydrogen of the pyridine ring of the dienophile.

Having ascertained that little was to be gained using diamine ligands, we extended the investigation to the effects of α -amino acid ligands. Since these ligands are chiral, this opens the possibility of enantioselective catalysis. To the best of our knowledge, in water no example of enantioselective Lewis-acid catalysis of a Diels-Alder reaction, nor of any other Lewis-acid catalysed organic reaction, has been published.

The influence of a large number of α -amino acids on the values of K_a and k_{cat} have been determined. These α -amino acids included: glycine, L-valine, L-leucine, L-phenylalanine, L-tyrosine, L-tryptophan, N α -methyl-L-tryptophan (L-abrine), N-methyl-L-tyrosine, N,N-dimethyl-L-tyrosine and p-methoxy-N-methyl-L-phenylalanine.

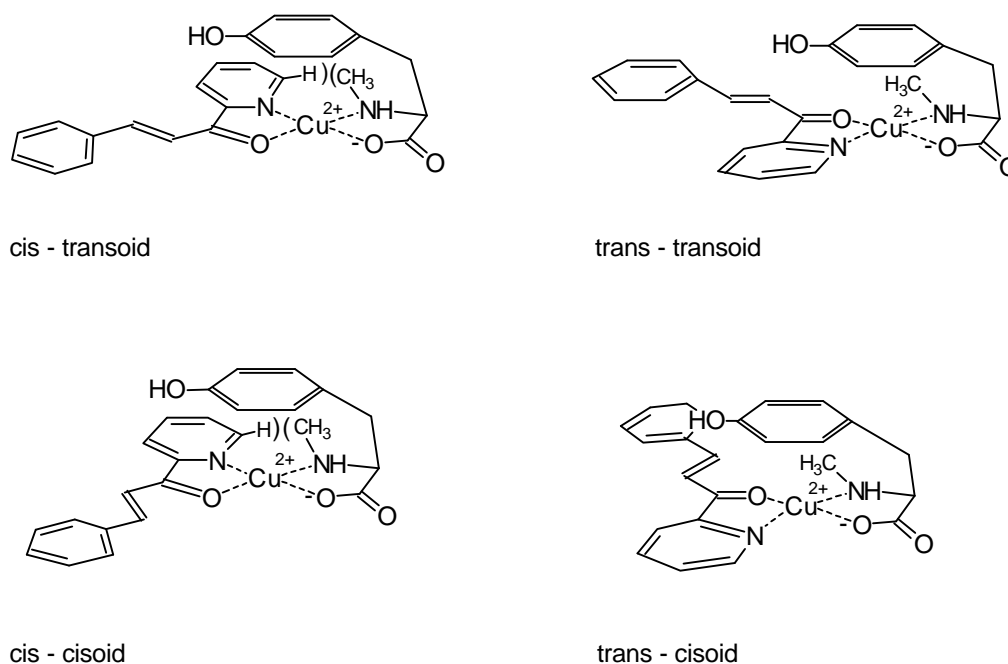
The effects of these ligands on the second-order rate constants for the $\text{Cu}^{2+}(\text{ligand})$ catalysed reaction of **1c** with **2** are modest. In contrast, the effects on K_a are more pronounced. The aliphatic α -amino acids induce an approximately two-fold reduction of K_a relative to K_a for the Cu^{2+} aquo ion. For the square planar coordinated copper ions this effect is expected on the basis of statistics. The bidentate ligands block half the sites on the copper centre.

Interestingly, when *aromatic* α -amino acid ligands are employed, these compounds can induce a more than four-fold increase of K_a relative to K_a for the Cu^{2+} aquo ion. The enhanced stability of the

ternary dienophile-Cu²⁺-aromatic α -amino acid complex is a result of an attractive interaction between the ligand and dienophile. Most likely an arene - arene interaction between the pyridine ring and the aromatic ring of the α -amino acid ligand is involved. This type of interaction is well-documented in aqueous coordination chemistry.

We envisaged that the arene - arene interaction may well shield one face of the dienophile from attack of the diene and consequently may induce enantioselectivity in this reaction. Indeed, in the presence of Cu²⁺(L-tryptophan), Diels-Alder adduct **3c** was obtained in 25% enantiomeric excess (ee). The enantiomeric excess can be improved to 74% by introduction of a methyl substituent on the α -nitrogen of L-tryptophan. The influence of the methyl substituent can be explained by considering the four different structures that can be envisaged for the ternary dienophile - Cu²⁺ - ligand complex (Scheme 2). These four structures result from two degrees of freedom: a cisoid - transoid equilibrium of the α,β -unsaturated ketone moiety in the dienophile and the possibilities of a cis and a trans geometry of the coordination environment around the copper(II) centre. Note that reaction of **1c** through the cis-transoid and trans-cisoid complexes results in (R,R)-**3c**, whereas reaction through the trans-transoid and cis-cisoid complexes produces (S,S)-**3c**. The methyl substituent on the α -amino acid further disfavours the cis geometry around the copper ion as a result of a steric interaction with the α -hydrogen atom of the pyridine ring of the dienophile. Consequently, the reaction mainly proceeds through the trans geometry resulting in an increase of the enantioselectivity.

We have investigated the effect of solvents on the enantioselectivity. It turned out that water (74% ee) favours the enantioselectivity of the Cu²⁺(L-abrine) catalysed Diels-Alder reaction between **1c** and **2** as compared to chloroform (44% ee), ethanol (39% ee), THF (24% ee) and acetonitrile (17% ee). The



Scheme 2

beneficial influence of water might well be a result of a favourable influence of this solvent on the strength of the arene - arene interactions.

Finally, we have investigated the nature of the arene - arene interaction. This interaction is enthalpy driven and counteracted by entropy. This observation indicates that hydrophobic interactions are not the major driving force, although these interactions will inevitably contribute to the strength of the arene - arene interaction in water. Examination of the influence of substituents in the dienophile on K_a demonstrated that the strength of the arene - arene interaction is not significantly influenced by electron withdrawing or donating substituents. Also the enantioselectivity of the reaction is not significantly influenced by substituents. This behaviour appears to rule out an important role of donor-acceptor interactions. We contend that the arene - arene interaction is mainly governed by London-dispersion interactions and electrostatic forces.

The fact that, for the first time, enantioselectivity is observed in an organic reaction catalysed by a chiral Lewis-acid in water opens new possibilities. First of all, since the arene-arene interactions, that are underlying enantioselectivity of the particular Diels-Alder reaction described in this chapter, are also held responsible for the enantioselectivity in many other reactions involving chiral catalysts, we infer that the enhancement of enantioselectivity by water might well be a general phenomenon. Hence, future water-promoted enantioselectivity of other organic transformations is envisaged. Moreover, the use of water facilitates mechanistic studies of catalysed reactions and can be expected to contribute to a deeper understanding of the interactions underlying enantioselective catalysis. The extensive knowledge and large set of techniques of coordination chemistry in water can now be successfully employed in enantioselective catalysis.

The work that is described in Chapters 2 and 3 involves the Diels-Alder reactions of diene **1**, that has been designed for bidentate coordination to Lewis-acid catalysts. The question arises whether the results obtained for this compound can be extended to other Diels-Alder reactions. This question is addressed in Chapter 4, in which attempts to catalyse Diels-Alder reactions of other potentially chelating dienophiles are described. Unfortunately, this approach was modestly successful. Apparently, coordination of organic molecules to Lewis acids in water is characterised by strict prerequisites. This conclusion called for an alternative approach of extending the scope of Lewis-acid catalysis of Diels-Alder reactions in water. We have made use of a strongly coordinating diamine auxiliary, which enables efficient coordination of the dienophile to the catalyst. A Mannich reaction is employed to covalently link the 2-(methylaminomethyl)pyridine auxiliary to benzylidene acetone as a model dienophile. Coordination of Cu^{2+} ion activated the adduct towards the Diels-Alder reaction with cyclopentadiene. Unfortunately, we did not succeed in the desired removal of the diamine auxiliary via a retro Mannich reaction. However, elimination of the diamine is possible, affording the Diels-Alder adduct which is functionalised by a vinyl group in 24 % overall yield.

Chapter 5 describes a study of the effect of micelles on the Diels-Alder reaction of **1** with **2**. Literature studies on micellar catalysis of Diels-Alder reactions invariably failed to reveal significant accelerations. These results are unexpected, since most Diels-Alder reactants have a high affinity for

micelles. Apparently binding of the reactants to the micelles does not lead to a significant acceleration of the reaction.

The results described in Chapter 5 provide an explanation for this intriguing behavior. This chapter describes a study of the effect of micelles of sodium dodecylsulfate (SDS), cetyltrimethyl-ammonium bromide (CTAB), dodecyl heptaoxyethylene ether ($C_{12}E_7$) and copper and zinc didodecylsulfate ($M(DS)_2$) on the Diels-Alder reaction of **2** with **1a-g**, containing neutral, cationic or anionic substituents. In the absence of catalytically-active transition-metal ions, micelles invariably retard the reaction. This can be rationalised on the basis of different binding locations of both reaction partners in the micelle. These binding sites have been probed using solubilisate-induced aromatic shifts on the 1H -NMR spectrum of the surfactant and paramagnetic counterion-induced relaxation enhancements of the 1H -NMR signals of the solubilisate.

These results can be extended to other Diels-Alder reactions. In view of the structures of most dienes and dienophiles a spatial separation of these compounds upon binding to micelles can be expected for the majority of Diels-Alder reactions. This arrangement most likely explains the unexpectedly small influence of micelles on the rates of Diels-Alder reactions as reported in the literature.

In contrast to SDS, CTAB and $C_{12}E_7$, $Cu(DS)_2$ micelles catalyse the Diels-Alder reaction between **1** and **2** with enzyme-like efficiency, leading to rate enhancements up to $1.8 \cdot 10^6$ compared to the reaction in acetonitrile. This results primarily from the essentially complete complexation of **1** to the copper ions at the micellar surface. Comparison of the partition coefficients of **2** over the water phase and the micellar pseudophase, as derived from kinetic analysis using the pseudophase model, reveals a higher affinity of **2** for $Cu(DS)_2$ than for SDS and CTAB. The inhibitory effect resulting from spatial separation of **1a-g** and **2** is likely to be at least less pronounced for $Cu(DS)_2$ than for the other surfactants.

We have demonstrated that due to inhomogeneous distribution of both reaction partners in the micelles, the pseudophase model leads to erroneous estimates of the second-order rate constant in the micellar pseudophase, so that conclusions regarding the medium of the reaction cannot be derived through this model. However, analysis of substituent effects and endo-exo ratios of the Diels-Alder adducts indicate that the reaction experiences a water-like medium.

In Chapter 6 we survey what has been accomplished and indicate directions for future research. Furthermore, we critically review the influence of water on Lewis acid - Lewis base interactions. This influence has severe implications for catalysis, in particular when hard Lewis acids and bases are involved. We conclude that claims of Lewis-acid catalysis should be accompanied by evidence for a direct interaction between catalyst and substrate.

Finally, we summarise our insight into hydrophobic effects that have developed during the work described in this thesis. The discussion focuses on the influence of hydrophobic effects on organic reactivity.

Katalyse van Diels-Alderreacties in water

In dit proefschrift staat één bepaalde chemische reactie centraal: de Diels-Alderreactie. Deze reactie dankt zijn naam aan de ontdekkers ervan, twee Duitse chemici: Otto Diels en Kurt Alder, die hiervoor in 1950 zijn beloond met de Nobelprijs. Het toekennen van de Nobelprijs geeft al aan dat het hier gaat om een belangrijke reactie. De Diels-Alderreactie vindt ook nu nog uitgebreid toepassing in de dagelijkse praktijk van de scheikunde, onder andere in de bereiding van talrijke medicijnen.

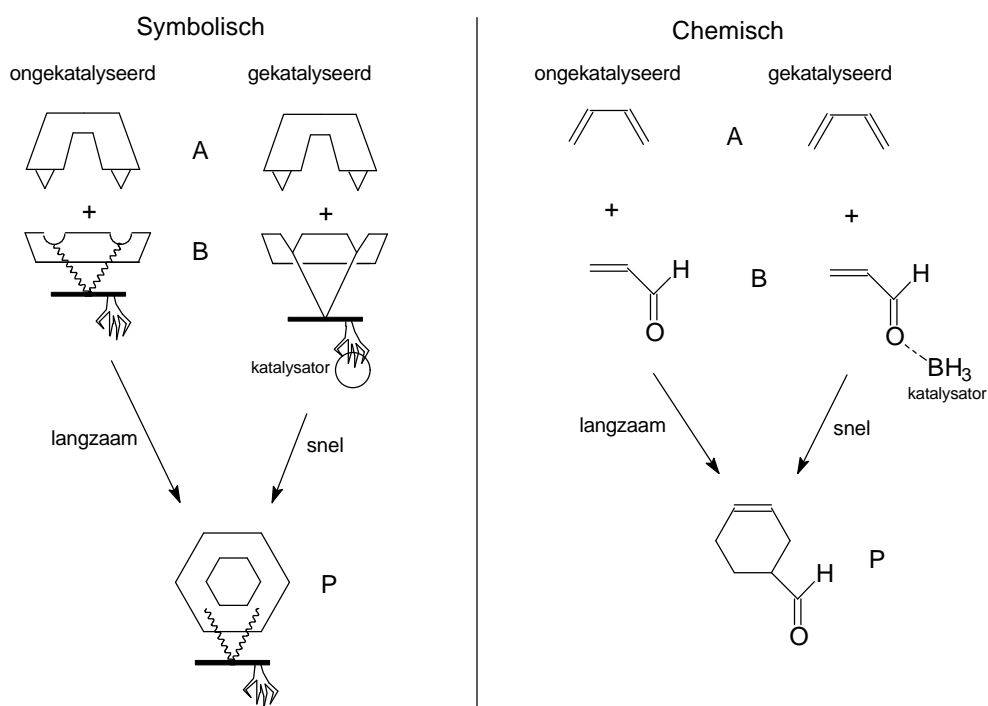
Hoewel de Diels-Alderreactie al bijna een eeuw bekend is, wordt er nog steeds veel onderzoek aan gedaan. De aandacht richt zich tegenwoordig met name op het vinden van methoden die het gebruik van deze reactie vergemakkelijken. Met vergemakkelijken wordt bedoeld het verkorten van de tijd die nodig is voor de volledige omzetting in het reactieproduct (het verhogen van de *reactiesnelheid* dus). Daarnaast is het van groot belang om de vorming van ongewenste bijproducten tegen te gaan. Deze bijproducten verontreinigen de gewenste stof die door de Diels-Alderreactie wordt geproduceerd en dienen na afloop van de reactie van de gewenste stof te worden gescheiden. Dit is vaak een lastige, kostbare en tijdrovende aangelegenheid. Het is dus van groot belang om tijdens de Diels-Alderreactie zo weinig mogelijk bijproducten te vormen. Met andere woorden, de *selectiviteit* van de reactie voor het gewenste product dient zo hoog mogelijk te zijn.

Het onderzoek, zoals dat beschreven is in dit proefschrift, had als doel methoden te vinden om de selectiviteit en de reactiesnelheid, twee belangrijke aspecten van de Diels-Alderreactie, te vergroten. Op beide aspecten zal dadelijk nader ingegaan worden.

Het onderzoek richtte zich vooral op het gebruik van water als oplosmiddel. Het was al een aantal jaren bekend dat juist water een gunstig effect heeft op zowel snelheid als selectiviteit van Diels-Alderreacties. Bovendien biedt het gebruik van water als oplosmiddel enkele belangrijke bijkomende voordelen. Binnen de chemie, zowel in de industrie als binnen de universiteit, tekent zich een ontwikkeling af in de richting van minder milieubelastende processen. Zo komt het gebruik van organische oplosmiddelen steeds meer onder druk te staan. Water vormt een milieuvriendelijk alternatief, dat, door de lage kostprijs, ook economisch aantrekkelijk is. Het is dan ook van belang om te weten to komen voor welke chemische reacties water als oplosmiddel gebruikt kan worden. Het onderzoek dat is beschreven in dit proefschrift hoopt hieraan een bijdrage te leveren.

Vergroten van de reactiesnelheid

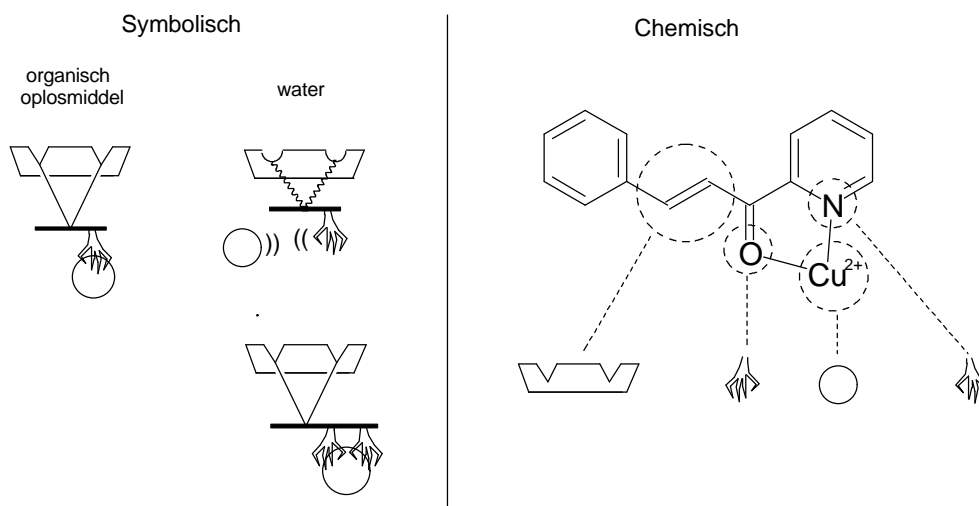
Het was uit de literatuur bekend dat Diels-Alderreacties sneller verlopen in aanwezigheid van een katalysator. Hoe dit in zijn werk gaat is schematisch weergegeven in de linker helft van Figuur 1. Hierin is een Diels-Alderreactie weergegeven tussen molekuul A en molekuul B die leidt tot de vorming van product P. Molekuul B is toegerust met een "handje" dat een katalysatordeeltje (vaak



Figuur 1

een metaal deeltje) kan "vastpakken". Wanneer het handje geen katalysatordeeltje heeft vastgepakt verloopt de Diels-Alderreactie langzaam. Wanneer er wel een katalysator wordt toegevoegd en vastgepakt wordt, verandert er iets (de elektronenverdeling, om precies te zijn) in molekuul B, waardoor de Diels-Alderreactie veel sneller verloopt. De rechter helft laat zien hoe dit proces wordt weergegeven in chemische structuren.

Daarnaast was het uit de literatuur bekend dat, wanneer water wordt gebruikt als oplosmiddel voor de Diels-Alderreactie, dit een gunstig effect heeft op de reactiesnelheid. In extreme gevallen kan de reactie in water tot 12.800 keer sneller verlopen dan in een organisch oplosmiddel. Het grote effect van water op de snelheid van de Diels-Alderreactie wordt voor een belangrijk deel veroorzaakt door het feit dat watermolekulen als katalysator kunnen optreden. Hierbij dient wel opgemerkt te worden dat watermolekulen zwakkere katalysatoren zijn dan de metaaliondeeltjes die meestal als katalysator worden gebruikt. Een tweede oorzaak van de versnelling van Diels-Alderreacties in water heeft te maken met het feit dat de meeste stoffen, die Diels-Alderreacties kunnen aangaan, weinig affiniteit hebben voor water. Wanneer deze molekulen (we zullen ze weer A en B noemen) de gelegenheid wordt geboden hun contactoppervlak met het omringende water te verkleinen, zullen ze daar "dankbaar" gebruik van maken. De Diels-Alderreactie biedt deze gelegenheid. A en B worden als het ware bijeen gedreven, waardoor ze gemakkelijker een chemische reactie kunnen aangaan. Dit is vergelijkbaar met het gedrag van twee oliedruppels in water. Ook deze zullen elkaar opzoeken en versmelten tot één druppel. Dit samendrijven van A en B gebeurt in organische oplosmiddelen niet, of in veel geringere mate, zodat de reactiesnelheid in organische oplosmiddelen kleiner is dan in water. Samenvattend waren er aan het begin van het onderzoek twee efficiënte manieren bekend om de



Figuur 2

snelheid van Diels-Alderreacties op te voeren: door het toevoegen van een katalysator en door water te gebruiken als oplosmiddel. Vreemd genoeg was nog niemand op het idee gekomen om te onderzoeken of deze twee methoden ook gecombineerd zouden kunnen worden. Dit zou tot een zeer grote toename van de reactiesnelheid kunnen leiden. Het eerste doel was dan ook het onderzoeken van het effect van katalysatoren op Diels-Alderreacties in water.

Het vinden van een Diels-Alderreactie die in water wordt gekatalyseerd, bleek echter niet eenvoudig. Daar waar in een organisch oplosmiddel het handje van molecuul B goed in staat is om een katalysator beet te pakken, bleek al vrij snel dat dit in water veel moeilijker en misschien zelfs wel onmogelijk is. Dit is toe te schrijven aan twee karakteristieken van water. Allereerst, zoals al eerder gezegd, is water zelf een (niet erg efficiënte) katalysator. Dat wil zeggen, het handje pakt ook graag een watermolecuul vast. Aangezien water het oplosmiddel is, zijn er veel meer watermolekulen dan katalysatormolekulen, met als gevolg dat het handje het grootste deel van de tijd een watermolecuul beet heeft. Bovendien hebben de watermolekulen de neiging om nogal stevig aan de katalysatordeeltjes te hechten. Het handje van molecuul B is niet "sterk" genoeg om deze watermolekulen van de katalysator te verwijderen.

Kortom, katalyse van Diels-Alderreacties in water met stoffen met maar één handje lijkt geen haalbare kaart. Echter, wanneer er twee handjes aan molecuul B gezet worden, zijn deze handjes samen wél in staat om een katalysatordeeltje in plaats van een watermolecuul vast te pakken. Figuur 2 geeft dit schematisch weer. De rechter helft van Figuur 2 laat een molecuul zien dat twee handjes bevat (een zuurstof- en een stikstofatoom) die samen een katalysatordeeltje (in dit geval een koperion) binden. Dit molecuul neemt een centrale plaats in in dit proefschrift.

In eerste instantie is de snelheid van de Diels-Alderreactie van dit molecuul (B2) met molecuul A2 (zie Figuur 3) bepaald in organische oplosmiddelen en in water, zonder en met katalysator. Bij de bepaling van de reactiesnelheid wordt gebruik gemaakt van het feit dat B2 gekleurd is, terwijl product P2 kleurloos is. De snelheid waarmee de kleur van het reactiemengsel verdwijnt is een maat voor de

Tabel 1. Halfwaardetijden voor de Diels-Alderreactie van B2 met A2 onder verschillende omstandigheden

	oplosmiddel	katalysator	halfwaardetijd ^a
organisch	-acetonitril	geen	1.6 jaar
	-ethanol	geen	7 maand
water		geen	48 uur
water met micellen		geen	53 - 58 uur
organisch	-acetonitril	koperionen	5 min.
	-ethanol	koperionen	15 min.
water		koperionen	4 min.
water met micellen ^b		koperionen	28 sec.

^a Tijd nodig om de reactie voor 50 % te laten verlopen

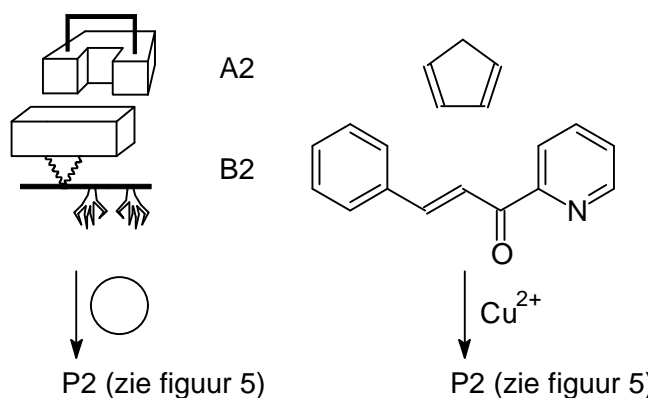
^b Micellen van natriumdodecylsulfaat (SDS)

snelheid waarmee de reactie plaatsvindt.

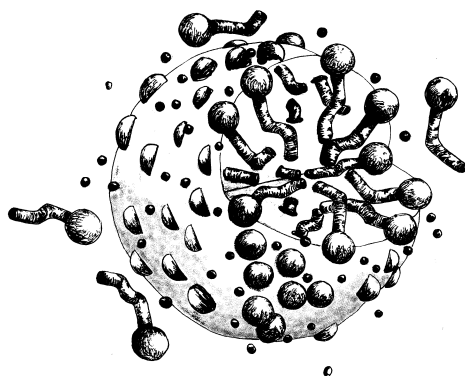
De belangrijkste resultaten van de snelheidsmetingen zijn samengevat in Tabel 1. Onder bepaalde condities doet de reactie zonder katalysator in het organische oplosmiddel acetonitril er 1.5 jaar over om voor 50% te verlopen. Onder dezelfde condities is de reactie in water zonder katalysator binnen 2 dagen voor de helft klaar. Wanneer koperionen als katalysator aan water worden toegevoegd, is de Diels-Alderreactie al binnen 4 minuten voor de helft verlopen. Dit geeft duidelijk aan dat het gebruik van een katalysator in water kan leiden tot een enorme toename van de snelheid.

Naast metaaliondeeltjes als katalysatoren, is ook de invloed van micellen op de reactiesnelheid bestudeerd. Uit Tabel 1 blijkt dat de reactie het snelst verloopt in aanwezigheid van zowel katalysator als micellen.

Om dit te kunnen begrijpen is enig inzicht in de eigenschappen van micellen vereist. Micellen zijn opgebouwd uit zeepmolekulen. Het speciale van zeepmolekulen is dat deze bestaan uit twee delen (een kop en een staart) met nogal verschillende eigenschappen. De kop heeft een grote affiniteit voor water, terwijl de staart juist het contact met water vermijdt. In water hebben de staarten dan ook de



Figuur 3



Figuur 4

neiging om samen te klonteren. De koppen voorkomen dat dit leidt tot de vorming van één grote druppel. In plaats daarvan worden een groot aantal zeer kleine druppeltjes (micellen) gevormd. De structuur van een micel is schematisch weergegeven in Figuur 4.

Eén van de bijzondere eigenschappen van micellen is het feit dat ze in staat zijn allerlei verbindingen die slecht in water oplossen aan zich te binden. Hierop berust bijvoorbeeld de waswerking van zeep. Micellen blijken ook in staat tot het binden van de molekulen A en B die de Diels-Alderreactie met elkaar aangaan. Op grond hiervan was te verwachten dat de Diels-Alderreactie sneller zou verlopen in aanwezigheid van micellen. Micellen zouden immers de reactanten bij elkaar brengen. Een significante versnelling van een Diels-Alderreactie door de aanwezigheid van micellen was echter nog nooit waargenomen. Ook uit de gegevens in Tabel 1 blijkt dat, wanneer micellen worden toegevoegd aan water (in afwezigheid van een katalysator), dit slechts een klein effect heeft op de snelheid van de Diels-Alderreactie. De beperkte literatuur over dit onderwerp bood hiervoor nog geen goede verklaring.

Studies, zoals die beschreven zijn in Hoofdstuk 5 van dit proefschrift, wijzen er echter op, dat micellen de molekulen A2 en B2 op verschillende plaatsen opnemen. A2 bevindt zich voornamelijk midden in het micel, terwijl B2 de voorkeur geeft aan de buitenkant. Het is dan ook niet verwonderlijk dat micellen de Diels-Alderreactie niet versnellen.

Wanneer er echter een katalysator aan de miceloplossing wordt toegevoegd, dan kan dit veranderen. Uit Tabel 1 blijkt duidelijk dat er in aanwezigheid van SDS micellen samen met een katalysator een zeer snelle Diels-Alderreactie kan optreden. In 33 seconden is de helft van de reactie verlopen. Voorwaarde is wel dat het type micel slim wordt gekozen. Van groot belang daarbij is de aard van de kopgroep. Wanneer ervoor gezorgd wordt dat deze een negatieve lading draagt (zoals in de SDS micellen), dan worden de positief geladen katalysatordeeltjes hierdoor aangetrokken en zullen deze zich ophopen in de buurt van de kopgroepen aan de buitenkant van het micel. Aangezien ook molecuul B2 een voorkeur heeft voor de buitenkant van het micel, is de binding van de katalysator aan B2 zeer efficiënt. Ondanks het feit dat de molekulen A2 zich nog steeds voornamelijk binnenin het micel bevinden, leidt de aanwezigheid van SDS micellen in combinatie met katalysatordeeltjes tot een enorme versnelling van de Diels-Alderreactie. Vergeleken met de reactie zonder katalysator leidt

dit tot een toename in snelheid met een factor 1.8 miljoen! Een dergelijke versnelling kan zich meten met het katalytisch effect van enzymen, de paradepaardjes onder de katalysatoren.

Een grote beperking van het gebruik van water als oplosmiddel voor gekatalyseerde Diels-Alderreacties is het feit dat er naar alle waarschijnlijkheid twee "handjes" nodig zijn om tot katalyse te kunnen komen. Hieraan valt wel een mouw te passen, wanneer men een aantal extra chemische reacties uitvoert, waarin eerst een tweede handje aan het molecuul B wordt gezet, daarna de gekatalyseerde Diels-Alderreactie wordt uitgevoerd en tot slot het tweede handje weer wordt verwijderd. Hoofdstuk 4 van dit proefschrift beschrijft een dergelijke aanpak.

Verbeteren van de selectiviteit

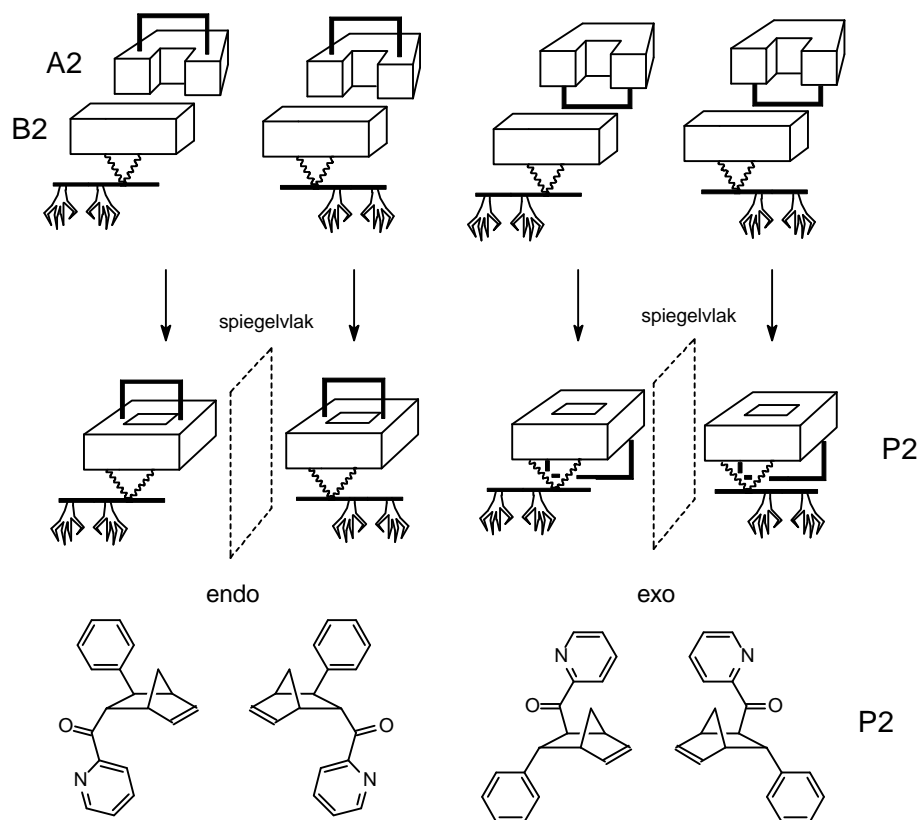
Een tweede doel van het onderzoek was het verbeteren van de selectiviteit van de Diels-Alderreactie. De vorming van ongewenste bijproducten dient zo veel mogelijk te worden voorkomen.

In de eerste plaats gaat het daarbij om producten die gevormd worden door andere reacties die zich tegelijk met de gewenste Diels-Alderreactie voltrekken. Wanneer de Diels-Alderreactie van B2 met A2 in water wordt uitgevoerd, onder invloed van een katalysator, is dit proces zo snel, dat andere ongewenste reacties weinig tijd hebben om een significante hoeveelheid bijproducten te genereren. In organische oplosmiddelen duurt de reactie langer, waardoor er meer tijd is voor de vorming van deze bijproducten.

Ten tweede kunnen er tijdens de Diels-Alderreactie meerdere producten worden gevormd. Voor de specifieke Diels-Alderreactie die in dit proefschrift uitgebreid is bestudeerd, worden er maar liefst vier verschillende producten gevormd. Deze producten lijken erg op elkaar. Ze zijn opgebouwd uit precies hetzelfde aantal koolstof-, waterstof-, zuurstof- en stikstofatomen. Het enige verschil tussen deze verbindingen is hun ruimtelijke opbouw. De vier verschillende producten kunnen worden onderverdeeld in twee "endo" en twee "exo" producten (zie Figuur 5). Onder invloed van koperionen als katalysator bleek dat de Diels-Alderreactie in water voor 93% de twee endo-producten opleverde en maar voor 7% de exo-producten. We hebben ons in het onderzoek dan ook verder geconcentreerd op de endo-producten.

De twee endo-producten verschillen van elkaar in het feit dat ze elkaars spiegelbeelden zijn, net als een linkerhand het spiegelbeeld is van een rechterhand. Een groot deel van de eigenschappen van de twee spiegelbeeldproducten zijn identiek, net als de eigenschappen van linker- en rechterhanden. Een linkerhand is in principe net zo geschikt voor het oppakken van bijvoorbeeld een tennisbal als een rechterhand. Dit wordt echter anders wanneer het gaat om het hanteren van asymmetrische zaken zoals bijvoorbeeld handschoenen. Dit geldt ook voor chemische verbindingen die elkaars spiegelbeeld zijn. Ten opzichte van andere asymmetrische verbindingen zullen de twee spiegelbeelden zich wezenlijk anders gaan gedragen.

Dit is in het verleden pijnlijk duidelijk geworden in het geval van softenon. Ook deze verbinding komt in twee spiegelbeeldvormen voor en werd als 50:50 mengsel als medicijn voorgeschreven. Nu bestaan



Figuur 5

de meeste verbindingen in het menselijk lichaam voornamelijk uit één spiegelbeeldvorm (een kast vol met, bijvoorbeeld, alleen maar linker handschoenen). Dit heeft als gevolg dat de ene spiegelbeeldvorm van een medicijn vaak een heel andere uitwerking heeft dan de andere. In het geval van softenon had de ene vorm het gewenste effect als kalmeringsmiddel, terwijl de andere vorm leidde tot misvormde baby's.

Voor bepaalde toepassingen is het dus van groot belang dat er maar één spiegelbeeldvorm wordt gebruikt. Omdat beide spiegelbeeldvormen zo erg op elkaar lijken, worden tijdens de meeste chemische reacties 50:50 mengsels van beide vormen geproduceerd. Na de reactie moeten deze dan van elkaar gescheiden worden. Dit is vaak lastig en vooral erg duur. Het zou dan ook beter zijn wanneer er maar één spiegelbeeld gevormd wordt. Hierbij komt weer de katalysator om de hoek kijken. Wanneer de katalysator een "handschoen"-karakter heeft, dan kunnen de "vingers" van de chemische reactie zo gepositioneerd worden dat er, bijvoorbeeld, alleen maar "rechterhanden" geproduceerd worden.

Bij de aanvang van het onderzoek waren er al een groot aantal van dit soort "handschoen"-katalysatoren bekend. Deze zijn echter alleen effectief in organische oplosmiddelen. In water waren er van het type katalysatoren dat actief is in de Diels-Alderreactie geen voorbeelden bekend die leidden tot de vorming van, bij voorkeur, één van de spiegelbeelden.

In de loop van het onderzoek zijn we een katalysator op het spoor gekomen die wel zijn

“handschoen”-activiteit behoudt in water. Het bleek zelfs dat de Diels-Alderreactie van B2 met A2 in aanwezigheid van deze katalysator in water een veel grotere voorkeur laat zien voor de vorming van één spiegelbeeldvorm van het product dan in organische oplosmiddelen. De succesvolle katalysator bestaat uit het al eerder genoemde koperion, met daaraan gekoppeld één spiegelbeeldvorm van een α -aminozuur¹.

Nabeschuwing

Na afloop van vier jaar onderzoek rijst natuurlijk de vraag: "Wat hebben we geleerd?". Zij die de wetenschap vanuit een wat breder perspectief benaderen, zullen ook vragen: "En wat kun je ermee?".

Om met de eerste vraag te beginnen: het onderzoek heeft de vragen die voor aanvang gesteld waren op bevredigende wijze beantwoord. Katalyse van Diels-Alderreacties in water is mogelijk en kan leiden tot een dramatische toename van de reactiesnelheid. Bovendien hebben we (voor het eerst) waargenomen dat water een gunstig effect kan hebben op de voorkeur voor één spiegelbeeldvorm.

Wat kun je daar dan mee? In de eerste plaats is het nuttig om inzicht te hebben in de mogelijkheden en onmogelijkheden met betrekking tot het overschakelen van organische oplosmiddelen op water als oplosmiddel.

Belangrijker echter, is de ontdekking van het gunstige effect van water op de voorkeur voor één spiegelbeeldvorm van het Diels-Alderproduct. Dit zou best wel eens een belangrijke stap voorwaarts kunnen zijn. Er zijn namelijk goede aanwijzingen dat niet alleen de Diels-Alderreactie, maar ook andere reacties in dit opzicht een gunstig effect van water kunnen ondervinden. Dit kan bijdragen aan, bijvoorbeeld, een efficiëntere productie van medicijnen.

¹ α -Aminozuren vormen overigens ook de bouwstenen van de meest efficiënte katalysatoren die er zijn, de enzymen.

STELLINGEN

1. Er wordt binnen het onderzoek aan homogene katalyse te weinig aandacht besteed aan stabiliteitsconstanten van de complexen van de katalysator met liganden, reactanten en producten.
2. De volharding waarmee wordt gerefereerd naar een publikatie van Viaene et al. als ondersteuning voor het belang van aren – ammoniumioninteractie voor micellaire systemen, terwijl juist in deze publikatie de relevantie van een dergelijke interactie in twijfel wordt getrokken, rechtvaardigt het gebruik van de term “Oostindisch blind”.
Viaene, K.; Verbeeck, A.; Geladé, E.; De Schryver, F. C. *Langmuir*, **1986**, 2, 456.
Shobha, J.; Srinivas, V.; Balasubramanian, D. *J. Phys. Chem.* **1989**, 93, 17.
Grieser, F.; Drummond, C. J. *J. Phys. Chem.* **1988**, 92, 5580.
3. De plannen tot invoering van een beurzenstelsel voor promovendi getuigen van een schromelijk gebrek aan waardering voor deze beroepsgroep en een onderschatting van de waarde van hun werk voor het functioneren van universiteiten op het terrein van zowel onderzoek als onderwijs.
4. De suggestie dat het geactiveerd complex van een chemische reactie ooit direct experimenteel zal kunnen worden waargenomen, gaat ten onrechte voorbij aan het feit dat er onderscheid gemaakt zal moeten kunnen worden tussen dit geactiveerd complex en alle andere structuren op de reactiecoördinaat, die veel talrijker voorkomen dan het geactiveerd complex.
Hoz, S.; *Acc. Chem. Res.* **1993**, 26, 69.
5. Het woord “hydrofoob” is in letterlijke zin meer van toepassing op organisch chemici, dan op de organische moleculen waarmee ze werken.
6. Autokatalytische systemen, waarbij de katalysator wordt gevormd uit molekulen die de katalysator als eenheid in zich dragen, hebben beperkte relevantie in relatie tot ons begrip van de evolutie.
Veronese, A.; Luisi, P. L. *J. Am. Chem. Soc.* **1998**, 120, 2662 en referenties daarin.

7. Gezien de opvoedkundige rol van de televisie in de huidige maatschappij, is een beperking van de invloed van kijkcijfers op het programma-aanbod wenselijk.
8. De auteurs die water modelleren als een verzameling van Mercedes Benz logo's, hanteren een oppervlakkige benadering.
Silverstein, K. A. T.; Haymet, A. D. J.; Dill, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 3166.
9. Het beleid gericht op natuur- en milieubescherming pakt slechts symptomen aan, zolang het terugdringen van de groei van de wereldbevolking niet in de beleidsdoelstellingen is opgenomen.
10. Publikaties, zoals die van Gottlieb et al., omvattende een weinig wetenschappelijke, maar zeer nuttige compilatie van NMR data van veel voorkomende organische verontreinigingen, verdienen navolging.
Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *21*, 7512.
11. Een bouwonderneming, die zich er op voorstaat de "ruimte voor morgen" te verzorgen, bezigt een eenzijdige benadering.
12. Water is hard.

S. Otto, 8 mei 1998.