Chapter 6

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 $^1$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 Cu(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 reaction$^1$. 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 $\text{H}_3\text{O}^+$. 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 state. 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 shells\(^3\). 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
important\textsuperscript{4}. 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 bonds\textsuperscript{5}. 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 change\textsuperscript{6}.

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 cosolutes\textsuperscript{7}. The effect on reactivity has been analysed by comparing the interactions between initial state and cosolute with those between transition state and cosolute\textsuperscript{7}.

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\(^7_{a,b}\). 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 place\(^9\). 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 system\(^10\) and that there is evidence for hydrogen bond formation to aromatic systems\(^11\). 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 deadlock. The occurrence of a reverse chelate effect has been reported for these systems, which can lead to more pronounced selectivities in binding of monodentate compounds.

It might also be possible to employ the hydrophobic effect for selective binding of a reactant to the catalyst. Interestingly, Menger et al. 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. 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 \( \eta^2 \pi \)-coordination to the carbonyl group of an \( \alpha,\beta \)-unsaturated ketone can be achieved, this would be a breakthrough, since it would subject monodentate reactants to catalysis by hard Lewis acids.

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 in 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.

Notes and references


6 Filling of these cavities with a nonpolar molecules is enthalpy driven. See: Diederich, F.; Smithrud, D. B.; Sanford, E. M.; Wyman, T. B.; Ferguson, S. B.; Carcanague, D. R.; Chao, I.; Houk, K. N. *Acta Chem. Scand.* 1992, 46, 205 and references cited therein


9 The type of enforced hydrophobic effect that is operative in the retro Diels-Alder reaction cannot be referred to an enforced hydrophobic interaction, since there is no coming together, but rather a separation of nonpolar molecules during the reaction. It is better to refer to this process as an enforced hydrophobic effect.


