Quantum Chemical Studies of Mechanisms and Stereoselectivities of Organocatalytic Reactions

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Abstract

As the field of organocatalysis is growing, it is becoming more important to understand the specific modes of action of these new organic catalysts. Quantum chemistry, in particular density functional theory, has proven very powerful in exploring reaction mechanisms as well as selectivities in organocatalytic reactions, and is the tool used in this thesis. Different reaction mechanisms of several organocatalytic reactions have been examined, and we have been able to exclude various reaction pathways based on the calculated reaction barriers. The origins of stereoselection in a number of reactions have been rationalized. The computational method has generally reproduced the experimental stereoselectivities satisfactorily.

The amino acid-catalyzed aldol reaction has previously been established to go through an enamine intermediate. In the first study of this thesis the understanding of this kind of reactions has been expanded to the dipeptide-catalyzed aldol reaction. The factors governing the enantioselection have been studied, showing how the chirality of the amino acids controls the conformation of the transition state, thereby determining the configuration of the product.

In the cinchona thiourea-catalyzed Henry reaction two reaction modes regarding substrate binding to the two sites of the catalyst have been investigated, showing the optimal arrangement for this reaction. This enabled the rationalization of the observed stereoselectivity.

The hydrophosphination of α,β-unsaturated aldehydes was studied. The bulky substituent of the chiral prolinol-derived catalyst was shown to effectively shield one face of the reactive iminium intermediate, thereby inducing the stereoselectivity.

The transfer hydrogenation of imines using Hantzsch esters as hydride source and axially chiral phosphoric acid catalyst has also been explored. A reaction mode where both the Hantzsch ester and the protonated imine are hydrogen bonded to the phosphoric acid is demonstrated to be the preferred mode of action. The different arrangements leading to the two enantiomers of the product are evaluated for several cases, including the hydride transfer step in the reductive amination of α-branched aldehydes via dynamic kinetic resolution.

Finally, the intramolecular aldol reaction of ketoaldehydes catalyzed by guanidine based triazabicyclodecene (TBD) has been studied. Different mechanistic proposals have been assessed computationally, showing that the favoured reaction pathway is catalyzed by proton shuttling. The ability of a range of guanidines to catalyze this reaction has been investigated. The calculated reaction barriers reproduced the experimental reactivities quite well.
7. Guanidine-Catalyzed Intramolecular Aldol Reaction

7.1 Guanidines as organocatalysts

7.2 Mechanistic study of the TBD-catalyzed intramolecular aldol reaction

7.3 Regioselectivity

7.4 Catalyst screening

7.5 Conclusions

8. Summary and General Conclusions

Acknowledgements

References
List of Included Papers

I.  *Density Functional Theory Study of the Stereoselectivity in Small Peptide-Catalyzed Intermolecular Aldol Reactions*
    
    Peter Hammar, Armando Córdova and Fahmi Himo

II. *Enantioselective Organocatalytic Hydrophosphination of α,β-Unsaturated Aldehydes*
    
    Ismail Ibrahem, Ramon Rios, Jan Vesely, Peter Hammar, Lars Eriksson, Fahmi Himo and Armando Córdova

III. *Organocatalytic Asymmetric Hydrophosphination of α,β-Unsaturated Aldehydes: Development, Mechanism and DFT Calculations*
    
    Ismail Ibrahem, Peter Hammar, Jan Vesely, Ramon Rios, Lars Eriksson and Armando Córdova

IV. *Density Functional Theory Study of the Cinchona Thiourea-Catalyzed Henry reaction: Mechanism and Enantioselectivity*
    
    Peter Hammar, Tommaso Marcelli, Henk Hiemstra and Fahmi Himo

V. *Phosphoric Acid Catalyzed Enantioselective Transfer Hydrogenation of Imines: A Density Functional Theory Study of Reaction Mechanism and the Origins of Enantioselectivity*
    
    Tommaso Marcelli, Peter Hammar and Fahmi Himo

VI. *Origin of Enantioselectivity in the Organocatalytic Reductive Amination of α-Branched Aldehydes*
    
    Tommaso Marcelli, Peter Hammar and Fahmi Himo

VII. *Theoretical Mechanistic Study of the TBD-Catalyzed Intramolecular Aldol Reaction of Ketoaldehydes*
    
    Peter Hammar, Cynthia Ghobril, Alain Wagner, Rachid Baati and Fahmi Himo
    *Manuscript.*

VIII. *Structure and reactivity relationship studies for guanidine-organocatalyzed direct intramolecular aldolization of ketoaldehydes*
    
    Cynthia Ghobril, Peter Hammar, Sanjeevarao Kodepelly, Alain Wagner, Bernard Spiess, Fahmi Himo and Rachid Baati
    *Manuscript.*
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>B3LYP</td>
<td>Becke 3-parameter density functional</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>CD</td>
<td>Circular Dichroism</td>
</tr>
<tr>
<td>CPCM</td>
<td>Conductor-like Polarizable Continuum Model</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBN</td>
<td>1,5-diazabicyclo[4.3.0]non-5-ene</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric Excess</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl, 2,4,6-trimethyl phenyl</td>
</tr>
<tr>
<td>MTBD</td>
<td>N7-methylated TBD; 1,3,2,6,7,4,8-hexahydro-1-methyl-2H-pyrimido[1,2-a]pyrimidine</td>
</tr>
<tr>
<td>OTMS</td>
<td>trimethyl silyl ether</td>
</tr>
<tr>
<td>PES</td>
<td>Potential Energy Surface</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>PMPNH₂</td>
<td>para-anisidine</td>
</tr>
<tr>
<td>QM/MM</td>
<td>Quantum Mechanics/Molecular Mechanics</td>
</tr>
<tr>
<td>R, S, Re, Si</td>
<td>Descriptors of stereochemistry</td>
</tr>
<tr>
<td>ROESY</td>
<td>Rotating-Frame NOE Spectroscopy</td>
</tr>
<tr>
<td>SCF</td>
<td>Self-Consistent Field</td>
</tr>
<tr>
<td>SCRF</td>
<td>Self-Consistent Reaction Field</td>
</tr>
<tr>
<td>TBD</td>
<td>1,5,7-triazabicyclo[4.4.0]deca-5-ene</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMG</td>
<td>1,1,3,3-tetramethylguanidine</td>
</tr>
<tr>
<td>ZPE</td>
<td>Zero Point Energy</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 General introduction

This thesis aims at giving insight into the reaction mechanisms and stereoselectivity of several organocatalytic systems. In recent years the field of organocatalysis has attracted wide interest and experienced a strong growth in research and development. By theoretical tools we can gain information in order to understand or verify predictions of the function of the catalyst. Thereby it is possible to refine the catalyst design or get ideas that can be brought over to other systems or catalysis of other reactions.

The work in this thesis explores the application of quantum chemistry, i.e. the use of quantum mechanics to derive physical properties of chemical systems, to obtain insight into chemical processes such as reaction mechanism and stereoselection. The method of choice is Density Functional Theory with the B3LYP functional, since it is well-studied and provides excellent trade-off between accuracy and computational speed suitable for the systems studied.

1.2 Stereochemistry

The structure of a molecule is defined by the connectivity and orientation in space of its atoms. Substances which contain the same kinds and numbers of atoms, i.e. the same molecular formula, but where these do not have the same connectivity are called constitutional isomers. Molecules with the same connectivity as defined by a two-dimensional map (A in Figure 1.1) but are different in the three dimensional space (Figure 1.1, B-D) are said to have different configuration and are called stereoisomers.

Stereoisomers can be characterized by two relationships, enantiomerism and diastereomerism. If two molecules are enantiomers they are mirror images of each other that cannot be superimposed by any rotation (structure B and C in Figure 1.1). Diastereomers have different connectivity in space. They are neither super-imposable on each other, nor are they mirror images (for example B and D or C and D in Figure 1.1). A common term for enantiomerism is chirality, referring to the Greek word for
hand ($\chi e$), since our hands practically are enantiomers. An equal mixture of two enantiomers is called a racemic mixture.

Constitutional isomers as well as diastereomers have physically different properties, such as for example melting point and different reactivity, and can be separated relatively easily. Enantiomers, on the other hand, have the same physical properties, except for interaction with polarized light. Classically, enantiomers have been characterized by their optical rotation, giving rise to the notion of optically active compounds. Optical rotation is the phenomenon of change in the plane of polarization when linearly polarized light passes through a medium where one enantiomer is in excess over the other. The linearly polarized light can be considered as an equal mixture of left and right circularly polarized light, which experience different refractive index in a medium comprising a non-racemic compound. This will shift the phase of the two components of the linearly polarized light, resulting in the optical rotation. Absorbance of circularly polarized light is also different depending on the chirality of the light and substance. This is used in the method called Circular Dichroism (CD), where the difference in absorbance of left and right circularly polarized light is measured for different frequencies.\textsuperscript{1}

Enantiomers interact differently with other chiral species, something that is exploited in the most common way of determining the enantiomeric excess. This is the use of high performance liquid chromatography or gas chromatography, which rely on chemical non-bonding interactions with enantiomerically pure stationary phases. Determination of absolute configuration can be achieved for example by X-ray

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{tartaric_acid}
\caption{A: Two-dimensional connectivity map of tartaric acid. B-D: Three dimensional representations. B and C are enantiomers. Either of B and C are diastereomers relative to D. The molecule D is a special case since it is identical to its mirror image, and is called a meso-compound.}
\end{figure}
crystallography, although this technique requires the incorporation of a heavy atom in the crystal\textsuperscript{2}, by comparison between experimental and theoretically calculated CD-spectra or by transformation into a compound with a known configuration. The study of enantiomers dates back to the mid-19\textsuperscript{th} century when Pasteur discovered optical rotation of enantiomerically pure tartaric acid.\textsuperscript{1}

1.3 Enantioselectivity

The main driving force for the development in stereochemistry, the study of stereoisomerism and in particular chiral molecules, is its need in applications such as development of pharmaceuticals, molecular biology, flavours and other food additives and agricultural applications.

Most large organic molecules in biological systems are chiral, including proteins and sugars. More importantly these molecules occur in only one enantiomer of which the specific configuration is required for correct interaction with other chiral molecules. In a few examples both enantiomers of a compound are naturally occurring, in which case the two stereoisomers most commonly have different biological activity. A few examples of this are aroma compounds such as carvone, found in caraway and spearmint.\textsuperscript{3} The molecules from caraway and those from spearmint are enantiomers. They come from different plants and have completely different smells. Limonene is another example where \textit{R}-limonene (one of the enantiomers) smells of orange while \textit{S}-limonene (the other enantiomer) smells of lemon. The importance of understanding and controlling stereochemistry can also be stressed by examples of pharmaceuticals. Thalidomide is probably the most well-known case, where one enantiomer combats pregnancy sickness. Unfortunately the other enantiomer caused birth defects.\textsuperscript{4} Another example is Naproxen, an anti-inflammatory drug. The \textit{R}-enantiomer is 28 times less active than the \textit{S}-enantiomer but more importantly the \textit{R}-enantiomer is reported to be a liver toxin, hence the drug has to be enantiomerically pure.\textsuperscript{5}

In order to achieve enantioselectivity, i.e. to obtain preferentially one of the two enantiomers from a reaction, the environment has to be chiral and non-racemic, creating a diastereomeric relationship between the substrate-chiral environment complexes which will enable the selection. This can be accomplished either by separating the enantiomers from each other by purification involving some chiral element, or already in the synthesis of the chiral molecule from achiral reactants. This latter method involves enhancement of the reaction rate leading to one enantiomer of the product, and is often termed enantioselective catalysis. Synthesis of chiral compounds is commonly called asymmetric synthesis. Either the catalyst or the reaction medium has to be chiral and non-racemic to achieve chirality in the product.
Another way of achieving single enantiomer substances is to synthetically modify natural products which are already enantiomerically pure.

1.4 Organocatalysis

Until recently two classes of catalysts have been successful in asymmetric catalysis, namely transition metal complexes with chiral ligands and enzymes. Enzymes often suffer from not being stable under synthetic conditions and are difficult or expensive to obtain in large quantities needed for large scale synthesis.\(^6\)\(^,\)\(^7\) They might also have a narrow substrate range and are hard to tune to the desired product. The metal catalysts commonly use the metal as a Lewis acid to bind electron rich segments of the substrate molecules. It is not uncommon that this binding is too strong, resulting in reduced catalytic turnover since the product remains bound to the catalyst. Also the price of metal catalysts is often high. A more serious problem of metal catalysis is that many metals are poisonous and require a lot of caution in order to handle toxic waste from chemical industry and expensive purification due to the strict requirements for pharmaceutical products.\(^8\)\(^,\)\(^9\)

The last decade a new class of powerful enantioselective catalysts has emerged, namely the use of chiral organic compounds as catalysts. This field is termed asymmetric organocatalysis and is the subject of this thesis. Among the advantages of using organocatalysts are their inertness towards moisture and oxygen, feasible reaction conditions such as ambient temperature and a large solvent scope. They are also inexpensive and often more stable than enzymes or other biomolecular catalysts.\(^9\)

The absence of metals makes the organocatalytic approach particularly attractive for applications where poisonous metallic traces are unacceptable in the final products, such as the pharmaceutical and agrochemical industries.

The concept of using asymmetric organic catalysts was in use already a century ago. A report of Breding and Fiske in 1912 where a small optical yield was obtained from addition of HCN to benzaldehyde in the presence of a cinchona alkaloid is regarded as the first example of asymmetric organocatalysis.\(^10\) Despite this long history the organocatalytic approach to enantioselective synthesis has largely been ignored, possibly due to the great success of organometallic catalysis.\(^11\) Not until the last decade there has been an incredible growth of interest in this field.\(^8\)\(^-\)\(^18\)

Figure 1.2 offers an overview of commonly occurring motifs in organocatalysis, selected from the viewpoint of this thesis. Organocatalysts can be either modified natural products or synthetic. The natural products are appealing since they are already chiral. One extensively used group of compounds are the cinchona alkaloids, such as quinidine (1-1) which is the base for the catalyst examined in Chapter 5. The natural
amino acids were also early identified as promising catalysts. Particularly, proline (1-2) is one of the most well studied compounds in this field. Catalysts based on amino acids or peptides are discussed in Chapter 3 and 4.

Organocatalysts can also be categorized according to their mode of interaction with the reaction partners. There are catalysts forming a covalent intermediate with the substrate. For example reactive iminium and enamine intermediates are formed by condensation of carbonyls to amine catalysts such as the ones considered in Chapter 3 and 4 for C-C and P-C bond forming reactions. Other catalysts work through hydrogen bonding or by transferring protons to and from the substrates. The catalysts used in the reactions of Chapter 5-7 are all of this latter class. In the C-C bond forming reaction studied in Chapter 5, the cinchona alkaloid (1-1) is functionalized with a thiourea (1-3), which is a frequently used hydrogen bond donor in organocatalysis. Another commonly occurring element is the 1,1'-binaphtol (BINOL), which provides a chiral scaffold since the binaphtol groups are hindered to rotate under ordinary reaction conditions. An example of a catalyst based on BINOL is the phosphoric acid 1-4, which promotes a hydrogenation reaction through deprotonation, hydrogen bonding and protonation, studied in Chapter 6. Finally, synthetic guanidine compounds such as TBD, 1-5, are used for promoting yet another example of organocatalytic C-C bond formation. Chapter 7 demonstrates how the guanidines act as proton shuttles in this reaction.

![Figure 1.2. Some common motifs in organocatalysis.](image-url)
2. Theoretical Methods

2.1 Introduction to Quantum Chemistry and Density Functional Theory

It is generally accepted that quantum mechanics, where physical observables are described as eigenvalues to mathematical operators, presently is the most accurate description of chemistry and chemical properties. This thesis deals with the feasibility of different reaction pathways. One way of addressing this is by considering their relative energy. Thus, the observable we are interested in is the energy \( E \), which is obtained as an eigenvalue to the Hamiltonian \( H \) operator, \( H \Psi = E \Psi \), where \( \Psi \) is the wave function that completely determines the chemical system. This is the time-independent formulation of the Schrödinger equation, and in the context of the chemical reactions studied here the time dependence of the original equation is neglected. To describe the energy in this context, the Hamiltonian includes terms of kinetic energy of nuclei and electrons, the attraction between electrons and nuclei and the electron-electron and nucleus-nucleus repulsions.

The first approximation to introduce at this point is what is known as the Born-Oppenheimer approximation, where the equation is separated in two parts, one concerning the electronic structure around spatially fixed nuclei, and one concerning the motion of the nuclei.\textsuperscript{19} This is rationalized by the presumption that the nuclei and electrons are moving on considerably different timescales. What will be discussed in the following section concerns the electronic part. The electronic wave function is a function of the spin and spatial coordinates of each electron and the methods available for solving wave function problems are typically very time-consuming for achieving acceptable accuracy. In this work we have employed density functional theory (DFT), where the problem is stated in terms of the total electron density. DFT is currently the best method for addressing problems like the ones considered in this thesis, as judged by computational time versus accuracy, given the computational resources available. Hohenberg and Kohn showed that the electron density uniquely determines the external potential (in a molecular case the charges from the nuclei), which in turn determines the ground state so that the ground state is completely determined by the density.\textsuperscript{20} The DFT approach results in a less demanding computational problem compared to wave function-based methods.
It is further proven that there exists a functional of the density such that its minimum value corresponds to the ground state energy. In order to calculate the energy, we need to know the density. One of the most helpful things in the search for the density is the variational principle presented by Hohenberg and Kohn\textsuperscript{20}, in which they show that the energy functional takes on its minimum value for the correct density, the value being the ground state energy. Finding the energy now reduces to minimizing a functional of the three-dimensional density function.

The minimization procedure employed is referred to as a self-consistent field (SCF) method, outlined for DFT by Kohn and Sham\textsuperscript{21} similar to the scheme used in the approximate wave function-based Hartree-Fock method.\textsuperscript{22} Kohn and Sham formulated the problem in terms of a system of non-interacting particles, and added all discrepancies compared to the real system in one term in the equations. Since the problem is expressed in terms of independent particles, the wave function can be expressed as a product of functions of one electron each, commonly called orbitals. Having an orbital representation, one may use variational calculus with Lagrangian multipliers, which transforms the expression for the energy into an eigenvalue problem for a one-electron operator, to minimize the energy. This one-electron operator consists of the operators of the energy of one-particle motion, nuclei-electron attraction, the repulsion from the total density and one term including all corrections compared to the real system of interacting electrons. Since the latter two terms are themselves functionals of the density, the problem is solved iteratively until consistency is reached. Initially the orbitals are constructed as a guess, from which the first one-electron operator is computed. Then a new set of orbitals are taken as the solution vectors with lowest eigenvalues of the equation and used for updating the operator, and the procedure is repeated until convergence is reached.

\textbf{2.2 Numerical Representation – Basis Sets}

The functional form of the one-electron function can be very complex, thus it is important to find an efficient way of representing it mathematically. Any function can be expressed as a linear combination of other functions spanning the same functional space (a complete set of basis functions), although possibly an infinite number of functions might be needed. In this way one can hope to find functions that are simpler to work with, so that although you need more of them it will be of good help. First we can note that we are studying functions of the spatial coordinates, which are practically limited in space, so that we can expect that a finite number of basis functions can be good enough. One popular choice of basis functions are atomic orbitals, i.e. the solutions to the one electron Schrödinger equation centred on the sites of the atomic nuclei are taken as basis functions. However, these functions have the computational drawback of having a radial part that decays exponentially, which is not very
convenient for computing derivatives. The exponential part of these functions can in turn be expanded in a basis of Gaussian functions, which have defined analytical derivatives and are computationally efficient. Each basis function is thus consisting of a polynomial multiplied by a sum of Gaussian functions. A basis set constructed in this way is called a Gaussian type linear combination of atomic orbital basis set. The use of this type of basis set has proven to give good results in quantum chemical calculations, and is the one that is used in the work summarized in this thesis. We can note that these functions are all centred on atomic nuclei, and practically limited in space, since the Gaussian function quickly tends to zero by distance.

In the projects of this thesis two sets of basis functions have been used. In the case of geometry optimizations the so-called 6-31G(d,p) basis set has been employed, where each core atomic orbital is expanded in terms of six Gaussians, and inner and outer components of the valence atomic orbitals are expressed by three and one Gaussian components, respectively. It also contains functions of higher orbital symmetry for both hydrogen (p) and other elements (d). This gives further freedom of displacing the electrons from their respective nuclear positions and one-electron orbitals, and is needed for expressing for example polarization of an atom. Energies are calculated using the larger and thus more accurate 6-311+G(2d,2p) basis set, having an extra function for the split valence, functions with a slower radial decay to represent a more diffuse electron distribution and additional polarization functions.

The procedure of different basis sets is used since the computational cost is related to the number of basis functions used. The geometry optimizations are computationally demanding, but the geometries achieved from calculations using the smaller basis set are accurate enough. For the energies more basis functions are needed to reach the demanded accuracy.23-25

2.3 The B3LYP Functional

As mentioned above, the functional used in the Kohn-Sham formalism of DFT includes the operators of the energy of one-particle motion (T), nuclei-electron attraction (V_{ne}), the repulsion from the total density (V_{ee}) and one term including all corrections compared to the real system of interacting electrons (F_{XC}), as summarized in Equation 1. The latter term thus includes the difference to the real kinetic energy arising from the electron interaction and all non-classical corrections to the electron-electron interaction, such as exchange, correlation and self-interaction. The major problem still today is that these contributions are unknown.

\[
E = T[\rho] + V_{ne}[z, \rho] + V_{ee}[\rho] + F_{XC}[\rho]
\]

The functional employed in this thesis is called B3LYP, and its non-classical term consists of several parts that are fitted to experimental data using three parameters, for
their respective weight into the final result. B3LYP is the most used density functional in chemistry, with a performance that rates among the best in numerous studies. The functional form includes an exchange energy that depends on the density, so called local density approximation \((E_X^{\text{LDA}})\), and also the density gradient with a functional form proposed by Becke \((E_X^{\text{B}})\) and one part consisting of the exchange energy as defined in the Hartree-Fock theory \((E_X^{\text{HF}})\) and a correlation functional proposed by Vosko, Wilk and Nusair \((E_C^{\text{VWN}})\) dependent of the density itself and one of the gradient, as proposed by Lee, Yang and Parr \((E_C^{\text{LYP}})\), as expressed in Equation 2. The values of \(a\), \(b\) and \(c\) are 0.20, 0.72 and 0.81, respectively, which were actually optimized for the similar functional B3PW91. B3PW91 has a somewhat different expression for the correlation energy.

\[
F_{\text{corr}} = (1-a)E_X^{\text{LDA}} + aE_X^{\text{HF}} + bE_X^{\text{B}} + (1-c)E_C^{\text{VWN}} + cE_C^{\text{LYP}}
\]

In the method outlined above the spin of the electrons has been neglected. In the systems studied in this thesis the electronic structure is so called closed shell, where all electrons are paired. As such there is no need for describing the spin, and a representation of the geometric distribution of each pair of electrons is enough. In a system of open shell structure, where the electrons of opposite spin are not always paired, the spin dependence can be expressed by using two densities, one for each spin. The electronic energy obtained by the method outlined above is according to quantum mechanics not the true ground state energy. The lowest energy a system can possess is referred to as the zero point energy (ZPE) and corresponds to the lowest vibrational energy that the system can adopt (which is not zero). This is calculated from the second derivatives of the energy with respect to nuclear displacements from the stationary points, which gives the vibrational energy from the harmonic approximation. This energy contribution is added to the electronic energy to get the ground state energy. The vibrational analysis is performed with the same basis set as is used for the geometry optimization.

### 2.4 Solvation Model

The DFT calculations as expressed above give us the optimized molecular structures in vacuum, or commonly labelled gas phase, corresponding to the geometry at 0 Kelvin being devoid of vibrations. This might be quite far from the reaction conditions of the experiment we are comparing to, and the optimal procedure would involve calculating the molecular properties in a condensed phase. However, calculation of molecular properties, such as molecular geometries and energies, at a microscopic level in a condensed phase is a great challenge mainly due to the number of involved molecules. There are two ways of approaching this problem, one being to treat all molecules in
the solution explicitly, the other describing the solvent implicitly as a dielectric medium.\textsuperscript{32}

There are a couple of different models for an explicit treatment of solute-solvent interactions, which all share the principle of sampling a large number of (geometrical) configurations and from the properties of each of these configurations derive the entities of interest (such as ground state geometry or energy). Among these methods are Monte Carlo, where configurations are randomly generated, and molecular dynamics, where the configurations are generated from each other by following the gradient of the energy. The energies of the configurations are classically calculated using force fields parameterized in the nuclear coordinates. This method does not have the accuracy desired in this study, and there is no parameterization that accounts for bond breaking and bond formation. Thus it is not suitable for chemical reactions as the ones studied in this thesis.

However, the methods can also be used by a quantum chemical calculation at each configuration, such as first-principle molecular dynamics, or a divided scheme with the central part of the system calculated by quantum chemistry and the bulk calculated with classical force fields, known as quantum mechanics/molecular mechanics (QM/MM) approach. These calculations are however not feasible, since they would require a huge amount of quantum calculations since many configurations have to be evaluated in order to get statistical data of the system.

A conceptually different approach to the problem is using continuum models, where the solvent interaction is approximated with that of a dielectric continuum surrounding the quantum chemically modelled molecule. In this work the conductor-like polarizable continuum model (CPCM) has been used.\textsuperscript{33-35} A surface is constructed around the molecule as the outer part of intersecting spheres centred on the nuclei. The surface is then treated as a conductor, on which the charges from the molecule induce a polarization. The charge distribution from this polarized conductor in turn gives rise to an electric field that affects the electron density. The electronic structure is then iterated against this potential in what is called a self-consistent reaction field (SCRF) method, until convergence of the new density function is reached. The polarizable continuum is expected to account for stabilization similar to that of interaction from solvent molecules, although it cannot describe any specific interactions such as hydrogen bonding. The CPCM model is defined by the dielectric constant, i.e. the permittivity of the solvent, and other parameters, such as solvent molecular size which determines the radii of the spheres defining the model surface.

In the applications in this thesis the solvent interaction is calculated as the difference in electronic energy compared to that of an in vacuo calculation. The solvent effect is calculated with the same basis set as the geometry optimization. This interaction energy is added to the gas phase energy obtained from the calculation with larger basis
set. It has been demonstrated that the geometry is not significantly altered if the molecules were to be optimized in within the SCRF solvent model.\textsuperscript{35} For the studies involving the dipeptide catalyst (Chapter 3) and the cinchona thiourea catalyst (Chapter 5) the UFF model has been used. This model uses radial parameters from the Universal Force Field method for building the cavity, treating hydrogen explicitly whereas many other schemes for cavity construction let the hydrogen atoms be included in the larger spheres from the heavier atoms. The explicit hydrogen description is of good use since in these studies there are several transition states involving a proton transfer, where the proton is no longer covered by the larger spheres. In the other studies the United Atom Topological Model applied on atomic radii of the UFF force field, UA0, is used. This is the default setup in the Gaussian 03 program package, which is the program package employed for all calculations.\textsuperscript{36} Where the UA0 model is used, explicit spheres are added when necessary, for example in transition states with proton or hydride transfer.

2.5 Interpretation of the Energies

This thesis deals with considerations of mechanisms and stereoselectivity in catalyzed reactions. This section will briefly introduce how the calculated energies can be related to relevant measurements.

The potential energy surface (PES) defines the energy of each geometrical setup. The calculations are used to retrieve the stationary points of the electronic energy landscape, although the real PES also includes the entropic factors, the zero point energy and solvent effects. We assume that the stationary points on the obtained PES after addition of the zero point and solvent corrections sufficiently closely resemble the desired ones. A stationary point can be either a minimum, which is the conformation that is statistically most occupied, or a first order saddle point (called transition state), that is the highest point of the minimum-energy path connecting two minima. The energies of these points are used to get an overview of the PES. According to Maxwell-Boltzmann statistics, the probability of any given geometry is related to its energy as the inverse exponent of the energy divided by the temperature and the Boltzmann constant, as expressed in Equation 3, where \( Z \) is the so-called partition function, which is the sum of the exponentials of all states (geometries).\textsuperscript{37}

\[
\frac{N_i}{N} = \frac{e^{-E_i/k_BT}}{Z}
\]  

(3)

The PES is assumed to be populated according to the Boltzmann distribution, and the number of molecules that are at the transition state are related to the total number according to the inverse exponential of the energy difference divided by the temperature and the Boltzmann constant. In transition state theory a chemical reaction
rate \( (k) \) is determined by this exponential energy difference (Boltzmann constant, \( k_B \), replaced by the universal gas constant, \( R \), in a molar context) multiplied by a factor of \( k_B \), the temperature \( (T) \) and divided by the Planck constant \( (h) \) as expressed in Equation 4.\(^{19}\)

\[
k = \frac{k_B T}{h} e^{-\frac{\Delta E^T}{RT}}\]

(4)

The energies referred to here are the free energies, whereas the ones calculated in this thesis correspond to the enthalpies, the difference being an additional entropic term in the free energy. This term is neglected here.

In many of the studied reactions no accurate measurement of the kinetics has been performed, hence there is no estimate of the experimental barrier to compare to the theoretical one. It is still possible to determine whether the activation energies obtained are feasible under the experimental conditions. A rule of thumb is that a barrier of 18 kcal/mol corresponds to a reaction rate of 1 per second at room temperature, and every change of 1.4 kcal/mol will result in a 10-fold alteration in reaction rate (see Figure 2.1).

More interesting is to compare the stereoselectivities. According to the Curtin-Hammett principle the ratio of different products formed from rapidly interconverting intermediates is dependent on the difference of the absolute energies of the transition states, in accordance to their relative population.\(^{38}\) Thus we can relate the stereoselectivity to the calculated enthalpies. The stereoselective outcome of a reaction is commonly expressed as enantiomeric excess (\( ee \)), the excess of one enantiomer over the other as a percentage of their sum (Equation 5, brackets denotes concentrations of the enantiomers). The \( ee \) as a function of the difference in transition state energy is depicted in Figure 2.1.

\[
ee = \frac{[R] - [S]}{[R] + [S]}\]

(5)
2.6 Scope of the Method

It should be noted that the formalism behind DFT is non-approximate for calculating the *in vacuo* molecular ground state. It is in two ways approximations come in. Firstly, and most importantly, the correct expression for the electronic interactions is unknown. The variational principle only holds true for the right functional, thus approximate functionals can give both higher and lower energies compared to the desired ground state. Secondly, the choice of basis set for expansion of the solution introduces a source of error. This error can be minimized by using a more complete set of functions. The parameters in the B3LYP functional are fitted for a test set of small molecules.\(^\text{26}\) The systems studied here only include elements up to the second row, hence the method can be assumed to be a good choice. A common way of assessing the accuracy of a functional is to evaluate the mean absolute error in calculated energies compared to the experimental values of heats of formations, i.e. the enthalpy change upon
formation of a molecule into its standard state from the constituting elements in their standard state. A recent study comprising 633 organic molecules showed that this mean absolute error is 2.6 kcal/mol when some systematic errors are eliminated.\textsuperscript{25} This is in line with earlier studies, that have shown an error in heats of formation of 2-4 kcal/mol.\textsuperscript{23,39} More relevant to reaction barriers is the isomerization energy benchmark given by Tirando-Rives and Jorgensen\textsuperscript{25} comparing 34 isomerization energies involving hydro-carbons, nitrogen-containing and oxygen-containing molecules. This showed an average error of 2.2 kcal/mol (using the 6-31G+(d,p) basis set) and the error decreased upon increasing the basis set. However, a study by Kang and Musgrave comparing transition state barriers reports a mean absolute error of 3.3 kcal/mol for hydrogen abstraction reactions and 4.2 kcal/mol for non-hydrogen abstraction reactions.\textsuperscript{40} Thus the reaction energies calculated in this work are expected to have an error of a few kilocalories per mole. For the energy difference of stereoisomers that are calculated to assess the enantio- and diastereoselectivities the relative errors are expected to be subject to even more substantial cancellation of errors, giving the sub-kcal/mol accuracy needed for these studies (1 kcal/mol energy difference corresponds to 70\% enantiomeric excess at 25 °C as can be seen from Figure 2.1). This is best verified by the agreement of the calculated stereoselectivities with experimental ones as shown in the present thesis as well as in many other studies.\textsuperscript{41-47}

The calculated energy corresponds to the enthalpy, and entropic factors are neglected since the estimation provided by the calculations does not offer accuracy comparable to the electronic energy. In bimolecular reactions there are significant entropic contributions, but for the stereoselection and reaction pathway comparisons performed here the isomers of molecular complexes have similar binding and the differences in entropic energy are presumably small enough to be neglected.

As noted above, the stationary points are those of the electronic PES. The location of the stationary points of the true energy surface (including entropy, solvation and other corrections) could hypothetically differ, but this is expected not to be of importance and is not considered. A more severe problem in determining the shape of the PES is finding the global minimum, since the optimization method gives us a local minimum. In most cases there are several local minima and several saddle points. A major part of the practical effort in this thesis has been dealing with the search for the global minimum or rather the lowest transition state. This is best exemplified by the study of the dipeptide-catalyzed aldol reaction (Chapter 3), where a multitude of transition states were optimized for the reaction leading to the same stereoisomer and a scheme of varying different geometrical parameters resulted in finding the globally preferred transition state.
Since the uncertainties are of the same order of magnitude as the calculated energy differences for stereoselective transition states, we cannot expect to reproduce enantiomeric excesses to the percentage given by the experiments. However, the obtained values are indicating the energetic trend of the different geometric constraints, which in many cases can establish a rationale for the observed selectivity.
3. Peptide-Catalyzed Aldol Reaction

One of the most important milestones in the field of asymmetric organocatalysis is the discovery of the intramolecular aldol reaction catalyzed by the amino acid proline. The discovery was made by Hajos and Parrish\(^48\) and Eder, Sauer and Wiechert\(^49,50\) in the 1970’s, and has been used in the synthesis of steroids.\(^{51}\) However, it was not until 2000 when List, Lerner and Barbas demonstrated that proline and its derivatives are highly enantioselective catalysts for the intermolecular asymmetric aldol reaction between ketones and aldehydes that asymmetric enamine catalysis received an increased attention.\(^{52}\) Córdova and co-workers demonstrated that also primary amino acids such as alanine\(^53,54\) and dipeptides of such amino acids\(^55,56\) are capable of catalyzing this reaction (see Figure 3.1).

![Figure 3.1. The peptide-catalyzed aldol reaction investigated.](image)

The aldol reaction is an important reaction for forming carbon-carbon bonds. The starting materials are two carbonyl compounds of which one must possess an \(\alpha\)-proton. The catalysts, amino acids and peptides, are commercially available and economically attractive.

This amino acid and peptide-catalyzed aldol reaction is also significant from the evolutionary point of view. It is believed that this reaction can be one of the reactions counting for the formation of the homochiral starting material needed for life to evolve.\(^57-59\) Importantly, the small peptides, in contrast to the amino acids, catalyze the reaction stereoselectively also in water\(^56\), and can thus be regarded as the precursors to aldolase enzymes.\(^60,61\)
In the case of proline, there have been several theoretical studies on the reaction mechanism as well as stereoselectivity. It is now established that the catalysis is performed via an enamine mechanism, formed after condensation of the ketone on the nitrogen of the amino acid (see Figure 3.2). The aldehyde is coordinated to and stabilized by the carboxylic acid in the transition state where the C-C bond is formed to the enamine. The mechanism and selectivity for the alanine-catalyzed aldol reaction between benzaldehyde and cyclohexanone was studied computationally by Bassan et al.

![Figure 3.2. The enamine mechanism of the peptide-catalyzed aldol reaction, with the C-C bond forming transition state displayed.](image)

In this study we have focused on the stereoselectivity in the dialanine-catalyzed reaction between benzaldehyde and cyclohexanone (Figure 3.1). This is done by locating and comparing the transition states for the stereointroducing C-C bond forming step.

### 3.1 Stereoselectivity

The dipeptide differs from the amino acid in regard to its use as a catalyst in two important aspects. In the aldol reaction the amino acid is a bifunctional catalyst where the carboxyl group is donating a proton or at least a strong hydrogen bond and the nitrogen is involved in the enamine formation. The dipeptide has another functional group, namely the amide group of the peptide bond, which is important in the transition state binding. The other difference, which is more of a modelling aspect, is that the dipeptide has a significantly larger conformational freedom. Practically this means that there are many transition state structures for the desired reaction.
The preceding work by Bassan et al. on the alanine-catalyzed aldol reaction was a thorough study done by locating all possible transition states for the stereointroducing C-C bond forming step of the reaction. The primary amino acid has rotational freedom in the C-N bond, which is locked in the ring in the secondary amino acid proline. This gives catalytic access to both faces of the enamine, which is not the case in proline. In the case of the alanine-catalyzed reaction of benzaldehyde and cyclohexanone several geometry variations can be envisioned, all of which comprise the transition to the desired configuration of the product. The attack can be on the Si- or Re-face of the enamine by the Si- or Re-face of the aldehyde. The enamine can be syn or anti to the carboxyl group. The cyclohexene ring can adopt different conformations, as well as rotameric variations along the forming C-C bond. Including two ring conformations and two rotamers, it all together gives 32 unique transition states.

In the case of the dipeptide the conformational freedom increases, since in addition to the factors just mentioned, the peptide itself can take on different conformations and the carboxylic moiety can reach further away from the amino residue than what is possible in the amino acid, hence a larger rotameric freedom along the C-C bond can be achieved with retained stabilization or protonation of the developing alkoxide.

Instead of locating all transition states by all possible variations, we decided to explore each conformational variation by finding some representative transition states which have all conformations same except for the one investigated. Using this approach we have selected the lowest energy conformation by each variation and found the overall most accessible transition states for the four different configurations of the product. These transition states are shown in Figure 3.3.

In respect to the factors mentioned above, we can draw some conclusions about the overall most accessible transition state. The transition state provides stabilization of the emerging alkoxide anion of the aldehyde by several hydrogen bonds from the catalyst. In the case of proline, where the only hydrogen bond donor present is the carboxylic acid, the proton is transferred to the carbonyl concertedly in the C-C bond forming transition state. In the transition state of Figure 3.3 A there are additionally two hydrogen bond donors, the terminal amine and the peptide amide. This provides efficient stabilization of the anion, which makes the proton transfer from the carboxyl group to form the alcohol of the product very asynchronous. For transition state A in Figure 3.3 a separate proton transfer transition state was located. The two transition states and the intermediate in-between lie within 0.3 kcal/mol for large basis set energy including zero point vibrational contributions. However when solvation correction is added the barrier for the proton transfer disappears, resulting in a concerted reaction in solution.
Figure 3.3. Most accessible transition states leading to the four possible stereoisomers of the dipeptide-catalyzed aldol reaction. The optimal transition state, leading to the major product observed (A). Two transition states with the same energy are found leading to the enantiomeric $(R,S)$-product (B and C). D and E show the transition states leading to the diastereomers. The configuration of the product and the relative energies in kcal/mol are given. Distances of hydrogen bonds to the developing alkoxide, and the forming C-C bond are given in Å.
While the amine offers the ability of enamine formation that is the basis for the catalysis in the reaction, the asymmetric electrostatic stabilization of the aldehyde by the hydrogen bond donors in the transition state makes the reaction stereoselective. The tridentate coordination in the optimal transition state offers a significant energetic stabilization. Lack of any of these hydrogen bonds results in a higher transition state energy.

The face of attack is determined for the aldehyde by the steric repulsion between the two substrates. For catalyst conformations of reasonable energy, the attack by the opposite face of benzaldehyde would result in a strong repulsion between the two rings. The cyclohexene-enamine intermediate is preferentially attacked on the face that lacks the repulsion from the chiral residue of the first amino acid and provides stabilization from the terminal amine hydrogen bond, i.e. the anti enamine. In the optimal transition state the steric repulsions within the peptide backbone are minimal for offering additional two hydrogen bonds from the amide and the carboxyl groups.

From the different possible ring twists of the cyclohexene in the transition state, the half-chair that will lead to the chair product is the most stable one in all comparisons we have made. Other rotamers of the substrates than the one are not preferred since that would result in loss of one or more of the hydrogen bonds and a less optimal catalyst conformation.

3.2 Conclusions

Similarly to the studies of stereoselectivity for proline and alanine, we find that the diastereoselectivity is a consequence of the interaction between the two substituents – the rings are energetically optimized to be apart from each other – and not directly dependent on the catalyst. While in proline the enantioselectivity is due to the conformationally constrain of fixing the carboxyl on one face of the enamine, the alanine offers selectivity based on avoidance of the sterics between the chiral residue of the amino acid and the ketone substrate in the major transition state. This is also the case for the dialanine. The multidentate binding in the peptide may explain why selectivity is retained in water where it is not for the amino acids. The computational results are in agreement of the experimental enantiomeric excess.
Chapter 4

4. Hydrophosphination of α,β-Unsaturated Aldehydes

Chiral compounds incorporating phosphorus are important for many chemical applications. In asymmetric metal catalysts it is common to use phosphines as ligands, whose chirality accounts for the asymmetry of the catalyst. Phosphines are also used as organocatalysts, and phosphonates are valuable precursors in the synthesis of pharmaceuticals.\textsuperscript{66,67} This chapter deals with an organocatalytic approach of enantioselective formation of phosphorus-carbon bonds.

Here a prolinol derivative (4-1) is used as catalyst, offering iminium catalysis. The residue breaking the symmetry in the pyrrolidine is a bulky substituent shielding one face of the iminium intermediate – in contrast to the bifunctional catalyst proline where the carboxyl residue takes part in the reaction and steer the stereochemistry by hydrogen bonding. In the computational model the bulky group is a diphenyl-, (trimethyl-silyl-ether)-methyl (Ph\textsubscript{2}OTMS). For the modelling, the optimized reaction was used where the reactants are cinnamic aldehyde (4-2), the simplest aldehyde from the experimental substrate scope, and diphenyl phosphine (4-4), the only nucleophile that showed enantiomeric excess. The reaction is illustrated in Figure 4.1. The reaction was performed in CHCl\textsubscript{3}, as was used for the calculation of the solvent effect.

\textbf{Figure 4.1.} Prolinol-catalyzed hydrophosphination. The configuration of the product is determined in the transition state where the phosphine attacks the iminium intermediate.
In the computational study we have addressed the enatioselectivity of the reaction, thus focusing only on the stereointroducing phosphination transition state. The aldehyde adds to the prolinol and forms an iminium intermediate, which then reacts with the nucleophilic phosphine. We have investigated the conformational possibilities of the iminium intermediate, demonstrating that the $E$-trans-isomer is lowest in energy among the $E/Z$-cis/trans-isomers considered. However, the $Z$-trans-isomer has quite similar energy, 2.0 kcal/mol, suggesting that it could possibly offer a relatively accessible transition state (Figure 4.2).

![Figure 4.2. $E$-trans- and $Z$-trans-iminium intermediates. $Z$-trans-iminium is 2.0 kcal/mol higher in energy including solvent correction.](image-url)
4.1 Stereoselectivity

Several transition states were optimized for the phosphine addition. The diphenylphosphine can be aligned corresponding to the three different rotamers of the product along the P-C bond. The different rotameric transition states are shown to lie relatively close in energy, the difference is due to the different interactions between the phenyls of the phosphine and the phenyl of the cinnamic iminium species.

The transition state holding the lowest energy is the attack of the unshielded face of the E-trans-iminium (Figure 4.3 A), which also gives the same stereoisomer as the experimentally observed major product (S). The located lowest lying transition state for the minor product (R) (Figure 4.3 B) is 2.1 kcal/mol higher in energy and corresponds to the attack on the unshielded face of the Z-trans-iminium. Thus the energy difference of the transition states correlates well with that of the iminium conformations, both being close to 2 kcal/mol. The attack on the shielded face of the preferred iminium (Figure 4.3 C) is slightly higher in energy, 2.4 kcal/mol, due to the steric repulsion from the bulky group.

4.2 Conclusions

The shielding of one face of the iminium intermediate is efficient, and our study indicates that the selectivity is dependent on the energy spacing of the different iminium conformations.
Figure 4.3. Lowest lying transition states leading to S-product (A) and R-product (B and C). Relative energies are given in kcal/mol and the distances of the forming P-C bonds are given in Å.
Chapter 5

5. Cinchona Thiourea-Catalyzed
Henry Reaction

The Henry reaction, also called nitroaldol reaction, is the addition of nitroalkanes to ketones or aldehydes, discovered by Belgian chemist Louis Henry in 1895. The reaction is a powerful method of C-C bond formation, where the nitro group is useful for subsequent functionalization. The reaction introduces one or two new stereocenters in the product molecule. An asymmetrically catalyzed reaction was presented by Shibasaki in 1992. Recently Marcelli et al. developed a cinchona-based organocatalyst for the Henry reaction. The cinchona alkaloids are well known and frequently used organic catalysts, since they are readily available and inexpensive natural products. They exist in two pseudoenantiomeric forms, such as quinine and quinidine, which provide a basis for creating one catalyst for each enantiomer of the product. The catalyst used in this study incorporates the quinuclidinium of the cinchona, a base that can deprotonate the nitromethane, coordinate the reacting species through hydrogen bonding and finally protonate the product. Also a thiourea moiety is used for coordination by strong hydrogen bonding.

The reaction mechanism was first addressed, considering two binding modes of the substrates (see Figure 5.1). Also, the stereoselectivity was investigated, by locating possible transition states leading to the different enantiomers of the product.

The binding geometry of the substrates and the rigidity of the catalyst minimize the number of transition states to consider, compared to the earlier studies. We have found two pathways similar to a related study by Papai and co-workers and can also for the present reaction and catalyst confirm that both pathways are feasible. Several models have been considered, initially to reduce the computational effort. Additions to the model were made to verify its validity. Experimental verification of the computational model has also been carried out. The reaction was modelled with THF (dielectric constant $\varepsilon = 7.6$), the experimentally used solvent.
Figure 5.1. The cinchona thiourea-catalyzed Henry reaction. Two possible pathways in regard to catalyst binding have been studied.
Chapter 5

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Figure 5.2. The chinchona thiourea catalyst, small model 5-6 and larger model 5-7.

Figure 5.3. Optimized transition state for the deprotonation of nitromethane.

5.1 Reaction Mechanism

The mechanism, which is illustrated in Figure 5.1, is considered as deprotonation of nitromethane, C-C bond formation and protonation of the product as well as regeneration of the catalyst. In our study we show that this is an energetically accessible mechanism. The nitromethane is converted into an activated nucleophile through deprotonation by the quinuclidine base without aid of solvent, also yielding quinuclidinium as a hydrogen bond donating site. The optimized transition state is shown in Figure 5.3. The barrier for proton transfer is calculated to be 10.8 kcal/mol. As a second step the benzaldehyde is hydrogen bonded to the catalyst making it more susceptible for nucleophilic attack.
For the C-C bond formation there is shown to be two coordination modes possible. In the first (Pathway A) the nitromethide is coordinated to the quinuclidinium through an ion pair interaction, while the benzaldehyde is hydrogen bonded to the thiourea. In the second (Pathway B) the nitromethide is bonded to the thiourea, while the aldehyde is coordinated to the quinuclidinium. The optimal transition states for the nucleophilic attack of the two pathways are shown in Figure 5.4. The energies of the transition states are similar, there is only a small preference of 1.6 kcal/mol for Pathway A. Thus both mechanisms are energetically feasible, Pathway A have a total barrier of 12.5 kcal/mol compared to the nitromethide-quinuclidinium ion pair. The ion pair is the lowest point along the reaction, being 2.7 kcal/mol more stable than the reactants separate.

In the case of Pathway B the former benzaldehyde carbonyl is protonated once the carbon-carbon bond is formed. In the optimization of an ion pair intermediate the proton is automatically transferred from the quinuclidinium to the alkoxide. The product complex is very stable, -5.6 kcal/mol compared to the reactants, while the whole reaction is almost thermoneutral having a reaction energy of 1.2 kcal/mol.

Figure 5.4. Preferred transition states for Pathway A (left) and Pathway B (right), both leading to the S-product. Distances of hydrogen bond-like interactions and forming C-C bonds are given in Å as well as the relative energies (in kcal/mol) of the two transition states.
5.2 Stereoselectivity

An enantiomeric excess of 73% at most was achieved in the experiment at room temperature. This corresponds to an energy difference of ca 1 kcal/mol between the most accessible transition states for the different enantiomers. However, the selectivity is strongly dependent on the solvent, demonstrating that solvent interaction in the transition state might be of great importance. Computationally we reproduced the enantioselectivity for model catalyst 5-6 shown in Figure 5.2. The optimal transition states for Pathway A leading to the different conformations of the product have an energy difference of 1.1 kcal/mol and are shown in Figure 5.5. The small energy differences in the different transition states are mainly due to steric interactions between the phenyl of benzaldehyde and either the methoxy group of the quinuclidinium or the phenyl of the thiourea.

![Figure 5.5. Transition states for Pathway A leading to the different enantiomers of the product. Left (A) is the preferred transition state (S), right (B) is the energetically most feasible transition state for the R-product.](image)

To verify these calculations a larger model was constructed, catalyst 5-7 (Figure 5.2). In this model the CF$_3$ groups were added as well as a benzyloxy substituent replacing the methoxyl group of catalyst 5-6. The transition states were reoptimized for this model (Figure 5.6). Except a vinyl fragment in position 5 of catalyst 5-7 this catalyst resembles the catalyst used in the original paper by Marcelli et al. Despite higher experimental enantiomeric excess (89%), we could note that two transition states leading to different enantiomeric products carry very similar energies. The transition state leading to the S-product is still favoured, but only by 0.2 kcal/mol.
5.3 Conclusions

There are no strong interactions that account for the selectivity, but rather weak steric interactions between the benzaldehyde phenyl and the catalyst that can be overcome by solvent interactions. We can demonstrate the trend of the selectivity, but fail to quantify it due to the strong solvent dependence of the reaction. It is beyond the scope of the CPCM method used in our study to account for the solvent interaction.
1,4-dihydropyridines are efficient reducing agents widely used in nature, including the enzyme cofactors nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH). Synthetic analogues have been developed, originally to yield insight into the biochemical processes. Recently more effort has however been directed into finding synthetically useful applications of 1,4-dihydropyridines, in the context of the growing interest in organocatalysis. For transfer hydrogenation, several groups have recently employed Hantzsch ester 6-1a as the hydrogen source together with organic catalysts (Figure 6.1).\textsuperscript{73,74}

Achiral amines and chiral imidazolidinones have been used in the transfer hydrogenation of α,β-unsaturated aldehydes.\textsuperscript{75,76} For the reduction of imines Rueping recently found achiral Brønsted acids efficient as catalysts, of which diphenyl phosphate was found most efficient.\textsuperscript{77} This opened up for development of chiral phosphoric acid catalysts, derived from 1,1′-binaphtol (BINOL) such as 6-6 in Figure 6.2, where R is some bulky aromatic substituent.\textsuperscript{78-80} The best catalyst has R=2,4,6-iPr-phenyl. This reaction gives high asymmetric induction for a range of PMP-imines and similar substrates (N-arylimines). Many other examples of C=N bond reduction have followed from this development. This study is aimed at investigating the role of the phosphoric acid catalyst in promoting the reaction as well as controlling the enantioselection.
6.1 Mechanism of Transfer Hydrogenation of Imines

Although it has been suggested for other reactions that phosphoric acid catalysts have a dual functionality, in the case of this reaction it was regarded simply as a Brønsted acid. It would thus protonate the imine to form the more electrophilic iminium, and hence lowering the barrier for the hydride transfer. We have contrasted this conception with a bifunctional mechanism involving coordination of both the iminium and the Hantzsch ester to the phosphate. The first step, protonation of the imine, was found to be thermoneutral and proceed with a negligible barrier. For the hydride transfer, all together three coordination modes have been investigated. Firstly, a di-coordinated pathway was examined, where the imine is hydrogen bonded to one phosphate oxygen and the Hantzsch ester coordinates to the other free phosphate oxygen. Secondly, a mono-coordinated Lewis base/Brønsted acid pathway where both the iminium and the Hantzsch ester are coordinated to one site of the phosphate was studied. Finally, a
Brønsted acid pathway with only the iminium coordinated to the catalyst was evaluated. In the mechanistic study the achiral diphenyl phosphate catalyst and Hantzsch ester 6-1b were chosen as model.

![Image](image.png)

**Figure 6.3.** Transition states for the three reaction modes, di-coordinated (A), monocoordinated (B) and Brønsted acid (C). Distances in Å are given for the hydrogen bonds to the phosphoric acid, the transferring hydride and the iminium C=N bond. Relative energies are given under each structure. Schematic representation of each transition state is given for clarity.
Figure 6.3 shows the transition states for the different reaction pathways investigated. The di-coordination is preferred by 6 kcal/mol over mono-coordination and 10 kcal/mol over the simple Brønsted acid mechanism. The energy difference is mainly due to the stabilization of the developing charge on the dihydropyridine. The di-coordinated transition state has a favorable short hydrogen bond between one phosphate oxygen and the NH of the Hantzsch ester, the O⋯H–N distances are 1.62 Å and 1.06 Å. In the case of the mono-coordinated transition state this hydrogen bond is longer, 1.89 Å, resulting in less stabilization.

6.2 Stereoselection in Transfer Hydrogenation of Imines

To address the stereoselection of the reaction using chiral BINOL-derived phosphoric acid catalyst we chose to employ a slightly simplified molecular structure compared to the catalyst 6-6 of Figure 6.2, 6-8 (Figure 6.4), as a model catalyst, in order to speed up the calculations. The naphtyls were replaced with phenyl groups and the isopropyls were replaced with methyl groups in order to reduce the size and speed up the calculations.

Figure 6.4. Model catalyst used in the calculations for investigating the enantioselectivity.

Although Z-imine is calculated to be 2 kcal/mol higher than the E-isomer, it is commonly assumed that it is the E-iminium that receives the hydride. We argue however that the two structures are in fast equilibrium and accessible in the reaction medium. We indeed find that a transition state involving the Z-iminium is lowest in energy (structure A of Figure 6.6). Transition states for E-iminium are higher in energy, the one leading to the R-product is higher by 2.3 kcal/mol (structure C), and that leading to the S-product is 2.6 kcal/mol higher (structure D). The Z-(R) isomeric transition state is 2.3 kcal/mol higher in energy than Z-(S) (structure B of Figure 6.6). The Z-isomer fits better into the pocket of the catalyst, since in this case the bulky
phenyl group points away from the catalyst, leaving the small methyl on the inside. This is most apparent for conformation A of Figure 6.6, where the Re-face is exposed towards the site for dihydropyridine coordination. In the conformation where the Si-face is exposed, the PMP-group is forced to reside closer to the mesityl of the catalyst, giving rise to higher transition state energy. The transition states with E-iminium experience steric repulsion between either the phenyl or the PMP and the catalyst mesityl groups, rendering both pro-S and pro-R transition states close in energy, more than 2 kcal/mol above the Z-S transition state.

Reuping et al. have shown that phosphoric acid-catalyzed transfer hydrogenation is also applicable to 2-substituted quinolines, resulting in very high enantioselection (Figure 6.5).\textsuperscript{81} The tetrahydroquinoline 6-10 is achieved by a cascade hydrogenation involving 1,4-hydride addition, isomerization and 1,2-hydride addition. Only the last step, which determines the stereochemistry, is investigated here. In the experimental study, a catalyst with opposite stereochemistry compared to 6-6 and 6-8 was used. Thus, the S-tetrahydroquinoline found experimentally will correspond to the R-enantiomer in our computational study.

The quinoline structure 6-9 is similar to the imine 6-5. In this case the conformation around the nitrogen is locked into the quinoline, resembling the E-imine stereoisomer. The transition states for the 1,2-hydride addition to the 3,4-dihydroquinoline, shown in Figure 6.7, are indeed very similar to those of the E-imine, Figure 6.6 C-D. The main difference is that the PMP group in transition state E-(S) in Figure 6.6 C has rotated out of the plane of the imine in order to decrease the repulsion to the mesityl group of the catalyst, an adaption that is not possible in case of quinoline. Due to this increased steric repulsion in the Q-(S) transition state the enantioselection for the quinoline is high, in agreement with the experimental results.

\begin{figure}[h]
\centering
\includegraphics[width=0.6\textwidth]{transfer_hydrogenation.png}
\caption{Transfer hydrogenation of 2-phenyl-quinoline catalyzed by the enantiomer of 6-6.}
\end{figure}
Figure 6.6. Transition states for the hydride transfer using catalyst model 6-8. The chiral diaryl substituent of the phosphate is shown as sticks for clarity, whereas the phosphate, the dihydropyridine and the imine are shown with balls and sticks.
A $Q-(S)$ 3.6 kcal/mol

B $Q-(R)$ 0.0 kcal/mol

Figure 6.7. Transition states for the hydride transfer to quinoline with relative energies indicated.

6.3 Stereoselection in reductive amination of aldehydes

The enantioselective hydride transfer using Hantzsch esters and chiral phosphoric acid catalysts has also been applied to the reductive amination of $\alpha$-branched aldehydes via dynamic kinetic resolution.\textsuperscript{82} Imines are generated by condensation of aldehydes and $p$-anisidine, and they undergo fast racemization in presence of the phosphoric acid catalyst (Figure 6.8). Subsequently the imines are subject for the protonation and hydride transfer as described above. The hydride transfer does not create any chiral center in this case, but the hydride transfer to the two enantiomers of the imines will be catalyzed with different rates by the chiral phosphoric acid, and hence an excess of one of the enantiomers of the amines will be achieved. We have investigated the hydride transfer step, in order to explain the origin of enantioselection in the reaction.
A total of eight transition states have been investigated, corresponding to the different transition state conformations regarding attack on the Re- or Si-face of either of the imine bearing S or R configuration of the stereocenter and E or Z conformation around the imine double bond. The transition states are summarized in Figure 6.9 showing the similar catalyst-substrate binding as for the transfer hydrogenation of imines just discussed. The transition state having the overall lowest energy was found to be S-Si-E. This structure has the best conformation to minimize the steric repulsions between the substrate, the hydride donor and the catalyst. Another conformation, S-Re-Z (G in Figure 6.9), also carries a low energy, isenthalpic in gas phase but 0.9 kcal/mol higher when the solvation effect is accounted for. In this transition state the steric repulsion between the substituents on the α-carbon and the mesityl of the catalyst is decreased on the cost of adapting the higher energy Z-conformation. Swapping the proton and the methyl of the chiral center of transition state A, thus changing chirality, forces a rotation of the phenyl and increases the repulsion from the close mesityl. This gives rise to a rotation of the substrates in the catalysts pocket and increases the energy of the transition state by 3.3 kcal/mol, see structure C (R-Si-E) of Figure 6.9. Interestingly it was found that the lowest transition state for the R-isomer (R-Re-E, structure B) has an enantiomeric geometry compared to A regarding the iminium and the Hantzsch ester. The PMP-group is in this case closer to one of the bulky mesityl groups of the catalyst, which is the main interaction responsible for the 1.8 kcal/mol increase of energy compared to S-Si-E. This is good agreement with the observed enantiomeric excess of the reaction (96%).\textsuperscript{82}
Figure 6.9. Transition states and their relative energies for the hydride transfer in reductive amination of α-branched aldehydes.
6.4 Conclusions

The phosphoric acid-catalyzed transfer hydrogenation of imines and reductive amination of \(\alpha\)-branched aldehydes have been examined. For the transfer hydrogenation of imines using Hantzsch ester as hydride source it was demonstrated that the bifunctionality of the phosphoric acid is important for catalysis. In the preferred reaction pathway the imine is hydrogen bonded to one oxygen site of the phosphoric acid, while the Hantzsch ester is coordinated to the another site.

The enantioselection of chiral phosphoric acid catalysts was successfully reproduced by the computational model. The \(Z\)-conformer of the iminium fits better in the binding pocket of the catalyst than \(E\)-iminium. The transition state for hydride transfer to the \(Re\)-face of the \(Z\)-iminium, resulting in the experimentally observed \(S\)-enantiomer, was found to have least steric repulsion and thus having the lowest energy. In the case of hydrogenation of quinoline, the iminium is locked into \(E\)-conformation. The energies of the \(S\)- and \(R\)-transition states of the \(E\)-iminium have reversed order compared to the \(Z\)-iminium, why an alignment for hydride transfer to the \(Si\)-face is energetically preferred for quinolinium. The energy difference between the \(E\)-transition states is elevated due to the lack of rotational freedom in the quinoline.

The mechanism and stereoselectivity has for the Hantzsch ester hydrogenation of imines catalyzed by chiral phosphoric acids have also been studied computationally by Simón and Goodman, reaching to similar conclusions.\(^3\)

The hydride transfer in the reductive amination of \(\alpha\)-branched aldehydes, using the same catalyst, was also investigated. In this case the preferred transition state was found to involve hydride transfer to the \(Si\)-face of the \(E\)-iminium with \(S\)-configuration (in this case our study uses the opposite configuration of the catalyst compared to the experiment, where the \(R\)-configuration was the major product). The energy separation of the transition states reproduces the observed selectivity well.
Chapter 7

7. Guanidine-Catalyzed Intramolecular Aldol Reaction

The intramolecular aldol reaction catalyzed by amino acids and small peptides has already been investigated in the first chapter of results in this thesis. This section summarizes the results of our investigations on the intramolecular aldol reaction of acyclic ketoaldehydes (Figure 7.1). For this group of compounds a regioselective direct reaction has been previously reported using proline as catalyst. With 7-oxooctanal (7-1, n=2) the proline-catalyzed reaction gives solely isomer 7-2, whereas with 6-heptanal (7-4, n=1) the reaction yields both regioisomers 7-1 and 7-2 in a 1:1 ratio. Recently Baati and co-workers discovered that guanidine-based catalysts such as TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene, 7-5) promote the reaction with high yield, and only gives stereoisomer 7-1 for both n=1, and preferably gives 7-1 for n=2 and (7-1 and 7-2 in a 3:1 mixture).

![Figure 7.1. Intramolecular aldol reactions of acyclic ketoaldehydes catalyzed by proline (left path) and TBD (right path).](image)

7.1 Guanidines as organocatalysts

Guanidines such as TBD are often referred to as superbases due to their strong basic character. TBD as a catalyst has other advantages as well, such as being cheap and commercially available as well as working in absence of inert reaction conditions, otherwise often required for ionic bases. Guanidines have been shown to be effective catalysts for a number of reactions. For example, TBD (7-5) catalyzes reactions such as Michael and Michael-type reactions, nitroaldol reaction, the Witting reaction, the Horner-Wadsworth-Emmons reaction, P-C bond formation, cyclocondensation of acylhydrazines, and ring-opening polymerization of cyclic...
Guanidine-based chiral compounds are also widely explored as promoters for stereoselective reactions, although several of the reports only show moderate enantiomeric excesses. Especially the C$_2$-symmetric chiral bicyclic guanidine base with 5-membered rings, **7-6** (Figure 7.2, R=Ph, t-Bu or some other bulky group), has been shown to be efficient for many organocatalytic enantioselective transformations such as the Diels-Alder reaction$^{98}$, Strecker synthesis$^{99}$, isomerization of alkynoates to allenoates$^{100}$, TMS cyanation of aldehyde$^{101}$ and protonation of enolates$^{102}$. Monocyclic chiral guanidines have been successfully used to obtain high enantiomeric excesses in for example the Michael reaction$^{103}$ and epoxidation of chalcone$^{101}$. Chiral guanidine bases have also been used for kinetic resolutions (non-catalytic) in reactions such as asymmetric silylation of secondary alcohols, alkylative esterification, and azidation$^{101,104}$, as well as other reactions$^{90}$.

Despite the amount of reports using guanidine-based catalysts, there have been few mechanistic studies dedicated to a deeper understanding of the activity of these compounds. TBD is the most basic guanidine commonly used, the pK$_a^{105}$ of TBD, MTBD (N-methylated TBD, **7-7**), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) and TMG (1,1,3,3-tetramethylguanidine, **7-8**) in acetonitrile are 26.03, 25.49, 24.34$^{86}$ and 23.3$^{87}$, respectively. TBD is accordingly shown to be the most efficient among MTBD, TMG, DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and BDU for a number of reactions.$^{85,88,91,92,95}$ However, in many cases it has been found that the relative reactivities of different bases often are larger than the difference in basicity. For example, for the Michael-type reactions, TBD-catalyzed the reaction in a much higher pace than MTBD, DBU, DBN or TMG.$^{91}$ The large difference in reaction time between TBD and MTBD (5 min vs. 6 h in toluene at room temperature) was reduced when polar solvents such as methanol or acetonitrile were used, suggesting that the protonated TBD plays a role as a hydrogen bond donor in the catalytic cycle.$^{91}$ In the Strecker synthesis the N-methylated variant of **7-6**, was found totally inactive where the protonated form (**7-5**) showed high activity.$^{99}$ Thus, guanidines acting in a bifunctional mode have been proposed in a number of studies, either as hydrogen bonding or proton shuttle.$^{91,95,99}$

![Figure 7.2. Some common guanidine bases.](image-url)
The first computational mechanistic studies of reactions involving organocatalytic guanidines were reported for the ring-opening polymerization of cyclic esters, where TBD has been shown to be a very potent catalyst. The mechanism of this reaction has been investigated using DFT simultaneously by Rice and co-workers and by Simón and Goodman. Two mechanisms were considered, firstly one where the ester is covalently bound to the catalyst, followed by breakage of the ester C-O bond before the addition of the alcohol. This mechanism was contrasted with one that does not involve any covalent intermediate, but is stabilized by hydrogen bonding. The barrier for the latter mechanism, involving hydrogen bonding instead of a covalent intermediate, was found much lower in both studies. MTBD, lacking the ability to stabilize the developing oxyanion by hydrogen bonding in the transition state, but also lacking the ability of forming covalent intermediates, is 90 times less reactive than TBD.

Additional computational studies have been published, where guanidine-catalyzed reactions have been investigated. Tan and co-workers have studied the stereoselective addition of fluorocarbon nucleophiles, and investigated the reaction also with DFT calculations. The bicyclic chiral catalyst, \( R=t\text{-Bu} \), was used, giving excellent diastereomeric ratio and enantiomeric excesses. Firstly the \( \alpha \)-proton of the \( \alpha \)-fluoro-\( \beta \)-ketoester is transferred to the catalyst, after which the two carbonyls are coordinated to the two NH of the guanidinium forming a very stable ion pair. In the transition state it is however found that only one of the carbonyls of the ketoester form a hydrogen bond with the catalyst, the other NH of the catalyst is hydrogen bonding the electrophile, demonstrating the bifunctional mode of the guanidine catalyst.

Ma et al. investigated the TBD-catalyzed hydrolysis of acetonitrile computationally. The mechanism consists of a series of proton transfer steps, either where TBD abstracts a proton (forming an ion-pair) or shuttle protons concertedly.
Figure 7.3. Computationally investigated reaction mechanisms for the TBD-catalyzed reaction.
7.2 Mechanistic study of the TBD-catalyzed intramolecular aldol reaction

We have modeled two aspects of the guanidine-catalyzed aldol reaction. Firstly, we investigated the mechanism of the reaction as well as the regioselectivity, secondly different guanidines were tested experimentally and computationally as catalysts for the reaction. We proposed and examined three mechanisms, one where the catalyst works as a base/acid, another where the substrate is covalently bound to the catalyst promoting a base mechanism and the third where the substrate is bound and iminium-enamine tautomerism advances the reaction, similar to the mechanism for the amino acid-catalyzed reaction. The investigated reaction mechanisms are summarized in Figure 7.3.

For the base mechanism (Figure 7.3 A) it was found that TBD promotes an enolization of the substrate rather than acting as a Brønsted base. The barrier for the former was found to be 15.4 kcal/mol whereas the latter has a barrier of 22.1 kcal/mol. The transition states are displayed in Figure 7.4. The enolate-guanidinium ion pair collapses to enol and neutral TBD when the complex is optimized (in gas phase). The ions optimized separately have an energy which is 23.8 kcal/mol higher than the substrates. Although the ions are expected to lie close to the transition state, the lower energy for the transition state is due to the explicit stabilizing interactions that the ions exert on each other. The enolization, having a much lower barrier, is catalyzed by the two nitrogen sites of the catalyst, one acting as a proton acceptor and the other as proton donor, enhanced by the resonance created in the transition state which closely resembles the protonated guanidinium ion.

Since the ion pair is not formed, the second step of the reaction, the ring closure/C-C bond formation, is not a pure Bronsted acid step. Instead it was found that also this reaction passes through a transition state where the guanidinium structure is used to facilitate proton shuttling, from the enol to the former aldehyde. This transition state was found to have a very similar energy to that of the first step, with a barrier of 15.5 kcal/mol. The two transition states are shown in Figure 7.4.

The covalent intermediate 7-10 (Figure 7.3 B) was observed experimentally, and a hypothesis was thus formulated for a mechanism involving this structure. In this proposal, the intermediate would promote the enolization, whereas the ring formation would take place after breaking the covalent bond. We found that the formation of the covalent intermediate is a fast process, with a barrier of only 7.9 kcal/mol. The intermediate itself has an energy of 2.7 kcal/mol higher than the ketoaldehyde and TBD separate, which is low enough to be observed experimentally. However we have not been able to find any beneficial effect on the deprotonation barrier starting from the covalent intermediate compared to the enolization discussed above. Several
transition states were located, leading to either a zwitterionic structure or a covalently bound enol. However, all of them have significantly higher barriers than the base-catalyzed mechanism, with the lowest one being 24.1 kcal/mol. Also the involvement of a second catalyst molecule in the enolization step was investigated. The obtained barrier for a transition state similar to the one in the base/acid mechanism on the covalent intermediate was found to be 18.8 kcal/mol, equivalent to the sum of the barrier for the base/acid and the energy of the covalent intermediate. The transition state for breaking the covalent bond is 18.9 kcal/mol, similar to the 7.9 kcal/mol barrier for forward reaction plus the enol energy of 10.9 kcal/mol. We can thus not find any preference for the mechanism involving the covalent intermediate 7-10.

The last mechanism investigated (Figure 7.3 C) is the iminium-enamine mechanism well known from the amino acid-catalyzed aldol reaction. The reaction starts with a condensation step, where the ketone is bound to the free TBD amino-site and a water is lost. We imagined this would be a multistep process, initiated by C-N bond formation concerted with proton transfer from the adjacent nitrogen to the ketone oxygen. The transition state has a barrier of 15.8 kcal/mol, and the following covalent intermediate is 12.2 kcal/mol higher in energy than the reactants. In order to dehydrate to form the iminium an extra proton is needed. Although there is no obvious proton source in the reaction medium, one could imagine neutral TBD or its conjugated acid. The barrier for dehydration starting with a protonated covalent intermediate is 25.6 kcal/mol. The energy cost of protonating the covalent intermediate, which is already 12.2 kcal/mol higher than the reactants, should be added to this calculated barrier for the dehydration step to get the total barrier. Also the C-C bond forming step was investigated. The transition state was found to be 30.7 kcal/mol higher in energy than the iminium, and having a barrier of 49.8 kcal/mol compared to the enamine structure immediately preceding the transition state. Thus both the dehydration and the C-C bond formation have drastically higher than those of the base/acid mechanism, why the present mechanism can be ruled out. The big energy differences noted in this mechanism are due to the unfavorable transformation between different resonance structures. The iminium structure has two separate π-systems (the guanidine N=C and the iminium N=C) that breaks the guanidinium symmetry. Therefore it is higher in energy than the protonated first covalent intermediate (having the planar guanidinium) and the guanidinium-enamine structure (where the enamine C=C bond is independent of the guanidinium π-system).
7.3 Regioselectivity

The investigation of the mechanism has been conducted using the anti-product, since this is thermodynamically more stable. It was calculated to be 0.5 kcal/mol lower in energy in good agreement with the 3:1 \( \text{anti:} \text{syn} \) ratio experimentally observed for the product. However NMR-experiments showed that the syn-isomer formed faster than the anti, but the two interconverted to yield the 3:1 ratio. In order to rationalize this, the transition state leading to the syn-product was also located. It indeed turned out that this was lower in energy by 2.3 kcal/mol, mainly due to the more compact
arrangement regarding the carbonyl/alcohol positions, featuring a more optimal arrangement for the proton transfers to the TBD (Figure 7.5).

![Chemical structures](image)

**Figure 7.5.** A and B: syn- versus anti-products. C: Optimized transition state leading to the syn-product. D: Optimized transition state leading to the ketol 7-2.

As mentioned, the TBD-catalyzed reaction is selective towards ketol 7-1, whereas 7-2 was not observed (for n=1). In order to rationalize this regioselectivity the transition state leading to 7-2 was located, see Figure 7.5 D. The barrier for this transformation is 22.6 kcal/mol, 7 kcal/mol higher than the transition state leading to 7-1 (Figure 7.4 C). The barrier for the nucleophilic attack on the ketone is higher, since the ketone is less electrophilic compared to the aldehyde. The C-C bond is also shorter in the transition state, and the proton transfer to the alkoxide is earlier.
7.4 Catalyst screening

The initial experimental study investigated the ability of several bases (organic and inorganic) to promote the reaction. Among those were the guanidines 7-5 (TBD), 7-7 (MTBD) and 7-8 (TMG) (Figure 7.6), which showed very different reactivity (see Table 7.1). To explore the capability of substituted guanidines to catalyze the intramolecular aldol reaction a library of guanidines was synthesized and investigated experimentally and computationally.

Computationally, the transition states for the two steps of the base mechanism, i.e. the enolization and the C-C bond formation, have been located for the different catalysts displayed in Figure 7.6. The calculated barriers as well as the experimental yields and pK\textsubscript{a} values are summarized in Table 7.1.

![Catalysts Considered](https://example.com/catalysts.png)

**Figure 7.6.** Catalysts considered in the computational study.

The calculated transition states for all molecules bearing two available nitrogen sites are similar in structure to those of TBD (7-5). For MTBD (7-7), only having one nitrogen site available for base/acid catalysis, the transition state for the enolization is that of proton abstraction. The barrier was calculated to 21.6 kcal/mol, actually lower than the similar transition state of TBD since the MTBD transition state has the character of moving the proton from the $\alpha$-carbon to the enol oxygen, whereas the TBD transition state is a pure proton abstraction. Since the ion pair with the enolate and protonated guanidinium required to protonate the aldehyde in the C-C bond
forming step was not found stable, the transition state for the C-C bond formation was not considered. A 39% yield was experimentally observed after 72 hours, while the TBD-catalyzed reaction was completed after half an hour.

### Table 7.1. Results from structure-activity relation investigation.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Calculated barriers (^a)</th>
<th>(pK_a) (^b)</th>
<th>Expt. conditions</th>
<th>Expt. barrier (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enolization</td>
<td>C-C bond formation</td>
<td>Yield</td>
<td>Time [h]</td>
</tr>
<tr>
<td><strong>7-5 (TBD)</strong></td>
<td>15.4</td>
<td>15.5</td>
<td>&gt;14</td>
<td>94%</td>
</tr>
<tr>
<td><strong>7-7 (MTBD)</strong></td>
<td>21.6</td>
<td>-</td>
<td>&gt;14</td>
<td>39%</td>
</tr>
<tr>
<td><strong>7-8 (TMG)</strong></td>
<td>25.9</td>
<td>21.7</td>
<td>13.2</td>
<td>17%</td>
</tr>
<tr>
<td><strong>7-19</strong></td>
<td>18.2</td>
<td>16.6</td>
<td>11.1</td>
<td>0%</td>
</tr>
<tr>
<td><strong>7-20</strong></td>
<td>16.7</td>
<td>16.3</td>
<td>12.9</td>
<td>88%</td>
</tr>
<tr>
<td><strong>7-21</strong></td>
<td>16.0</td>
<td>17.0</td>
<td>13.2</td>
<td>80%</td>
</tr>
<tr>
<td><strong>7-22</strong></td>
<td>17.8</td>
<td>16.2</td>
<td>&gt;14</td>
<td>85%</td>
</tr>
<tr>
<td><strong>7-23</strong></td>
<td>17.2</td>
<td>14.9</td>
<td>&gt;14</td>
<td>81%</td>
</tr>
<tr>
<td><strong>7-24</strong></td>
<td>18.3</td>
<td>17.0</td>
<td>12.3</td>
<td>39%</td>
</tr>
<tr>
<td><strong>7-25</strong></td>
<td>18.7</td>
<td>16.2</td>
<td>&gt;14</td>
<td>58%</td>
</tr>
<tr>
<td><strong>7-26</strong></td>
<td>20.3</td>
<td>20.3</td>
<td>12.4</td>
<td>0%</td>
</tr>
<tr>
<td><strong>7-27</strong></td>
<td>20.0</td>
<td>20.3</td>
<td>9.8</td>
<td>0%</td>
</tr>
<tr>
<td><strong>7-28</strong></td>
<td>28.5</td>
<td>-</td>
<td>11.5</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(a.\) in kcal/mol.

\(b.\) Measured in MeOH/H\(_2\)O 80/20 mixture.

\(c.\) Estimated relative barrier from the experimental yields and timings:

relative barrier = 1.4 \log(a_{TBD}/a); \(\text{a : yield } = 1-e^{-a^d t}\) for yields and times \(t\) in the table.

In the case of tetramethylated guanidine (TMG), 7-8, the optimized transition state for both steps turned out to be of proton shuttling character to the same nitrogen site. In the case of the enolization transition state shown in Figure 7.7 A, TMG acts as a base abstracting the \(\alpha\)-carbon proton, although the guanidine proton will be concertedly delivered to the enolate oxyanion in the gas phase optimized transition state. The barrier is 25.9 kcal/mol, reflecting the lower \(pK_a\) of TMG compared to TBD and MTBD. For the C-C bond forming transition state, Figure 7.7 B, the geometry is more symmetrical regarding the proton positions, and the imaginary frequency of the transition state clearly shows that the reaction is concerted. The more strained geometry for the proton transfer together with the lower basicity of TMG results in a barrier of 21.7 kcal/mol for this step. Although the relative height of the barriers
compared to those of TBD suggest that the reaction will not be catalyzed by TMG under the same conditions, a small yield was observed after 72 hours (Table 7.1).

The presence of a five-membered ring in the bicyclic guanidines prevents the tertiary amine to attain a planar structure, reducing the delocalization of the electrons over the guanidine core. This geometric constraint has been established by X-ray diffraction data\textsuperscript{89} on the neural bicyclic guanidines 7-5, 7-19, 7-20 and 7-21 and is also in agreement with the calculated geometries. In Table 7.2 the degree of pyramidization of the tertiary nitrogen, i.e. how pyramidal the nitrogen is compared to the perfect tetrahedral arrangement, is reported. Experimentally measured values from the literature for the neutral guanidines and calculated values for the neutral guanidines, the corresponding cationic guanidiniums and the C-C bond forming transition state are presented. The cation of 7-5 (TBD) is planar, representing a high degree of delocalization of the charge throughout the guanidine core, and consequently has a very high $pK_a$. In contrast, the protonated form of the [3.3.0]-bicyclic guanidine 7-19 cannot adopt the planar structure, and the $pK_a$ is significantly lower.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.7.png}
\caption{Transition states for enolization (A) and C-C bond formation (B) with catalyst 7-8 (TMG).}
\end{figure}
Table 7.2. Influence on the tertiary nitrogen in bicyclic guanidines.

<table>
<thead>
<tr>
<th>Structure</th>
<th>{m,n} (^a)</th>
<th>DP% (^b) lit.</th>
<th>DP% (^c) neutral</th>
<th>DP% (^d) TS</th>
<th>Barrier (^e)</th>
<th>DP% (^f) cation</th>
<th>pK(_a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-5</td>
<td>{6,6}</td>
<td>0.1</td>
<td>8.8 (^g)</td>
<td>1.4</td>
<td>15.5</td>
<td>0.9</td>
<td>16.6</td>
</tr>
<tr>
<td>7-19</td>
<td>{5,5}</td>
<td>26.6</td>
<td>27.6</td>
<td>21.1</td>
<td>16.1</td>
<td>12.1</td>
<td>11.3</td>
</tr>
<tr>
<td>7-20</td>
<td>{6,5}</td>
<td>18.2</td>
<td>17.8</td>
<td>7.6</td>
<td>16.3</td>
<td>2.7</td>
<td>12.9</td>
</tr>
<tr>
<td>7-21</td>
<td>{7,6}</td>
<td>4.2</td>
<td>5.9</td>
<td>8.8</td>
<td>17.0</td>
<td>3.1</td>
<td>13.2</td>
</tr>
</tbody>
</table>

\( a. \) Number of atoms in the cycles.

\( b. \) Degree of pyramidization, defined as \([360° - (\alpha + \beta + \gamma)] / 0.9\) (see Figure 7.8 \(c\)) according to reference [89] from where the values also are collected.

\( c. \) Degree of pyramidization as calculated by DFT for the neutral catalyst structure.

\( d. \) Degree of pyramidization in the C-C bond forming transition state.

\( e. \) Barrier for the C-C bond forming transition state.

\( f. \) Degree of pyramidization for the cationic (protonated) guanidinium.

\( g. \) 8.8% refers to structure A of Figure 7.8. Structure B of the same figure is calculated to have a degree of pyramidization of 1.6%.

Figure 7.8. Optimized structures for TBD, 7-5. Structure B is calculated to be 0.6 kcal/mol less stable than A. Structure B was reported as the X-ray structure.\(^89\) C: definitions of the parameters presented in Table 7.2. D: definitions of the angles discussed in the text.

In the case of the transition states, the direction of the N-H or N⋯H bonds are important for optimal proton shuttling. In the enolization transition state the parallel alignment in TBD is preferred, the angle between the N-H and N⋯H is -2° (defined as \([\alpha-90°+\beta-90°]\) where \(\alpha\) and \(\beta\) are the H-N-N angles, see Figure 7.8 \(D\)). The angle in the cation of 7-5 is -6°. However, in the [3.3.0]-bicyclic 7-19, the angle is strained from the cationic one (26°) to a much smaller, 13°, and the barrier is 2.8 kcal/mol higher than for TBD. The transition state is shown in Figure 7.9. In contrast, in the C-C bond forming transition state, a longer distance is preferred to accommodate an optimal proton shuttling between the two carbonyls. The angle in TBD is increased to 7°, whereas that in 7-19 is 28° close to the cationic case, which is a contributing factor to the low barrier for this step (16.6 kcal/mol) despite the low pK\(_a\). Although the
calculated barriers are similar to those of catalyst 7-25, which showed a yield of 58% after 24 hours, no yield was detected for 7-19 after the same time.

The [4.3.0]-bicycle 7-20 that attains a quite planar structure in the transition state and has higher pKₐ than 7-19, has also lower barriers than 7-19, around 1 kcal/mol higher than that of TBD, in good agreement with the experiments. The larger [5.4.0]-bicyclic guanidine 7-21 was found to be slightly less reactive, in agreement with the experimental yield.

For the monocyclic guanidines as well as the asymmetric ones, there exist several conformers. In order to find the lowest energy conformation, an investigation of the conformations of the neutral catalysts was first undertaken. The results are presented in Figure 7.10. ROESY NMR experiments were conducted to confirm the most stable conformation of the catalysts 7-25 and 7-26. In the case of 7-25, the methyl groups were found to be in a syn position as in 7-25 c, which however was found less stable by 1.4 kcal/mol in the DFT calculations. On the other hand, for 7-26 the methyl groups were determined to have an anti relationship (corresponding to 7-26 a or b). This is in agreement with the calculations, which in this case show a larger separation between the syn- and anti-forms (see Figure 7.10).

**Figure 7.9.** Optimized transition states with catalyst 7-19 for the enolization (A) and the C-C bond formation (B).
The *syn*-structure is unproductive for a proton shuttle mechanism, and such a structure must therefore undergo conformational changes in order to align the two reactive sites for the reaction. The cost for this conformational change (\(a \rightarrow c\)) can, at least in part, be responsible for the higher transition state barrier obtained for the 5-membered ring guanidine 7-26, compared to that of the 6-membered 7-25. This is in agreement with the experimental findings for these catalysts, where 7-26 did not catalyze the reaction.

For the catalysts that do not possess \(C_2\)-symmetry, the two nitrogens that are involved in the proton shuttle do not have identical properties. To examine whether this has an influence on the nature of the optimal transition state the two possibilities were investigated. In the case of 7-22, the lowest energy conformer was found to be the structure with the double bond on the acyclic chain thus having a proton on the nitrogen in the ring. The structure having the proton on the acyclic chain nitrogen and the double bond in the ring is 2.8 kcal/mol higher in energy (structure \(c\)). The proton on the acyclic chain nitrogen is thus the more acidic one in the guanidinium cation, and the nitrogen in the ring is the most basic site between the neutral molecules 7-22 \(a\) and \(c\). An alignment where the nitrogen in cycle is arranged to abstract the proton from the enol and the NH in the acyclic side chain is directed to deliver the proton to the carbonyl in the C-C bond forming step would thus be optimal. This is found to be the case as transition state A of Figure 7.11 carries this relationship, whereas the transition state with opposite alignment, B of Figure 7.11, was calculated to be 1.1 kcal/mol higher in energy. A similar relation was found for 7-23, where the difference between the two structures (in this case \(b\) and \(c\)) is 0.4 kcal/mol and the transition state where the enol is hydrogen bonding to the basic nitrogen in the cycle (structure \(c\)) is the lowest one by 0.6 kcal/mol. In the last case investigated, 7-24, the difference between the catalyst conformers is 0.6 kcal/mol, whereas the transition states are almost degenerate.
Figure 7.10. Relative energies of different molecular structures of catalysts 7-20–7-27. The energies (in kcal/mol) are relative to the first (named) structure of each row.
Guanidine 7-24, containing a 5-member ring, has a lower pK\textsubscript{a} value than 7-22 and 7-23, and also shows higher calculated barriers, in agreement with the lower experimental reactivity.

The sulfur compounds, where no guanidinium resonance can be formed, have high barriers. The bicyclic 7-28 (see Figure 7.6) only possesses one site of catalysis, similarly to MTBD. The pK\textsubscript{a} difference suggests a lower reactivity for proton abstraction of 4 kcal/mol. However, the calculated barriers have a difference of 7 kcal/mol. The other sulfur containing base computationally investigated is the monocyclic molecule 7-27. The big difference between the monocyclic 7-27 and the bicyclic 7-28 is that 7-27 can provide the ability of proton shuttling. Although this compound is less basic than 7-28 by almost 2 pK\textsubscript{a}-units, the ability of proton shuttling renders the barrier for the enolization 8.5 kcal/mol lower than that for 7-28. The barrier is 1.3 kcal/mol higher for the enolization step compared to the guanidine catalyst most similar in structure, 7-25, and 4.1 kcal/mol higher for the C-C bond forming step. No reactivity was observed experimentally for any of the sulfur containing compounds.

![Figure 7.11](image)

**Figure 7.11.** Transition states for the C-C bond forming step catalyzed by 7-22. Transition state A has a barrier of 16.2 kcal/mol, whereas the barrier for B is 17.3 kcal/mol.
7.5 Conclusions

Three mechanisms have been investigated, demonstrating that the optimal reaction pathway involves hydrogen bonding in both the enolization step and the carbon-carbon bond forming step. Although a covalent intermediate was observed, it does not show any energetic advantage. A mechanism involving iminium-enamine tautomerism has very high barriers due to unfavorable transformation between different resonance structures. This is well in line with previous theoretical studies showing that guanidines act by dual hydrogen bonds or by shuttling protons.

We have accordingly shown that the bifunctionality of the guanidine catalysts is important in promoting the aldol reaction. Enolization is shown to be a concerted event, where abstraction of the α-proton of the ketone and protonation of the ketone happens simultaneously. Also in the C-C bond forming step there is a concerted proton transfer from the enol to the aldehyde. This result agrees well with observations of the relatively low reactivity of methylated guanidines.

A range of bicyclic, monocyclic and acyclic guanidines have been examined as catalysts for the intramolecular aldol reaction. The computationally attained reaction barriers are generally in good agreement with the experimentally observed reactivities. Several explanations for the difference in catalyst activity have been identified. The pK\textsubscript{a} of the catalyst is important, and is affected by the rigidity of the molecular structure. Thus the ring size of the cyclic guanidines is an important tuning factor in achieving a highly potent catalyst. Guanidines that do not have two sites available for a bifunctional catalyst mode show very high barriers and are not potent catalysts, no matter if the pK\textsubscript{a} is high or not. For the monocyclic (and probably some acyclic, which have not been investigated computationally) guanidines the conformational change required to attain two sites for proton shuttling in the same direction contributes to the transition state energy.
8. Summary and General Conclusions

Several organocatalytic reactions have been investigated in order to determine the reaction mechanisms and to explain the origins of stereoselection. Transition states have been optimized along different reaction pathways, and the calculated barriers were able to discriminate between different proposed mechanisms. All the catalysts studied, except the prolinol derivative used for the hydrophosphination reaction, are shown to be bifunctional, in the sense that two (or more) sites of the catalyst have bonding interactions with the substrates. In the peptide-catalyzed aldol reaction the ketone is reacts with the terminal nitrogen, and the aldehyde is hydrogen bonded by the peptide NH-bonds and carboxylic OH-bond in an optimal arrangement for attack from the enamine. The cinchona thiourea has two binding sites, the thiourea group which can donate two hydrogen bonds, and the quinuclidine moiety which becomes a hydrogen bond donor after abstracting a proton from the nitroalkane substrate. Each of the two substrates can bind any of the two sites, either way the barrier for carbon-carbon bond formation is quite similar. In the transfer hydrogenation, the hydrogen bonding of the hydride donor to one phosphoric acid site and the hydride acceptor to the other was shown to be energetically preferred. The transition states for the guanidine-based catalysts are stabilized by resonance formed in the guanidinium structure, which is taken advantage of in a proton shuttling by the two nitrogen sites of the catalysts.

The origins of stereoselection in a number of reactions have also been rationalized. In general we have seen that hydrogen bonding of the substrates is the key factor for aligning the reacting partners. The positioning of these hydrogen bond donors or acceptors is thus important for achieving a favourable barrier for the desired reaction. The stereoselection is then accomplished by steric repulsion between the substrates and different, often bulky, groups of the catalysts, which are placed in such a way that a chiral environment is created around the active site of the catalyst. In the peptide-catalyzed reaction the side chain of the N-terminal amino acid repels the ketone (that is bound to the amino acid) in the transition state leading to the enantiomer of the major product. Other factors are also the loss of stabilizing hydrogen bonds for certain
transition state conformations, as well as steric repulsion between the two substrates. In the phosphination of unsaturated aldehydes, a catalyst without hydrogen bonding capabilities was used. In this case the bulky group of the catalyst shields one side of the covalent intermediate from attack of the nucleophile. For the cinchona thiourea catalyst, the methoxy group of the quinuclidinium and the phenyl group of the thiourea repel the substrates. When both the Hantzsch ester and the iminium are hydrogen bonded to the phosphoric acid catalyst, a conformation exposing one of the faces of the molecule to the hydride donor is preferred, due to higher repulsion from the bulky groups of the catalyst for the other possible conformations.

The difference in energy between the lowest lying transition states leading to the different possible stereoisomers of the product determines the selection of the configuration of the reaction product. In practice a multitude of transition states with different conformations can be envisioned, of which many may have similar energies. This results in that even a study of a reaction with a relatively simple mode of stereoselection develops into an intricate investigation.

Optimizing the stereoselection of an organocatalytic reaction is often difficult. In reactions where the selectivity is controlled by bulky substituents, there is usually a trade-off between reactivity and stereoselection. Even if that is not the problem, the direct effects of the chirality of the catalyst, i.e. the repulsion from bulky groups, are circumvented by adopting different conformations. The diastereoselection for the amino acid and peptides originates for example from the repulsion between the substrates, which are aligned closely thus avoiding the repulsion from the catalyst. Hence the ordering of the transition states leading to different products may be altered upon change of the substrates. Similarly, the shielding of one face of the iminium by prolinol-derived catalysts is dependent of the iminium being restricted to adopt only the E-isomer. Modifying groups of the substrate or the catalyst will most likely alter the energy spacing between the E- and Z-iminium intermediates, which will affect the stereoselection. In the hydride transfer reaction studied, the high energy Z-isomer of the iminium turned out to be the conformation adopted in the transition state, since it fits better into the catalyst pocket.

Stereoselection is often governed by quite subtle effects. Large changes of the enantiomeric excess can be achieved by changing the energy spacing of the transition states by only a small amount. Consequently, alterations of the reaction conditions, such as switching from one solvent to another, can result in rather larger change in the stereoselection, which is also commonly observed. An enantiomeric excess of 90% represents a fairly small energy difference, around 1.5 kcal/mol at room temperature. This challenges also the accuracy of the computational methods suitable for studying organocatalytic reactions. We have however generally been able to reproduce the
experimental stereoselectivities satisfactorily in the reactions studied. DFT has also proven very powerful in exploring reaction mechanisms in organocatalytic reactions. The in-depth understanding obtained by computational studies regarding the mode of action of different catalysts, both concerning reactivity and selectivity, is important for the design of new and improved organic catalysts, as well as development of wider applications.
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References


105 $pK_a$ of the bases refers to their conjugated acids.


