



*Understanding the Role of Aqueous Solution in Chemical Reactions. A  
Computational Study*

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# Summary

## Motivation

Water is a unique solvent due its structure and reactivity. The ability of a water molecule to form hydrogen bonds is its most important characteristic. In liquid water, each molecule typically donates and accepts two hydrogen bonds. This structure significantly enhances water's ability to accept or donate protons. In addition, the lone pair electrons of the water oxygen can be involved in stronger bonds, for example when a water molecule acts as a ligand in a metal catalyst. Water is one of the most important solvents in (bio)chemistry. Due to its properties, solvent effects in aqueous chemical reactions are often significant. Both beneficial and negative effects of water in chemical reactions are well documented. Compared to the organic alternatives, water is an environmentally friendly, cheap and safe solvent. To date, the role of the solvent in aqueous chemical reactions is only partially understood. A full understanding on a detailed molecular level is often completely absent. This issue is the central theme of the present thesis where we report molecular simulation studies of two prototype aqueous chemical reactions. These reactions are not only of fundamental interest, but have also a significant importance in technological applications. In our study we employed molecular simulation of an accurate atomistic model, yielding a detailed picture of the structure and dynamics on the molecular level. The outcome provides important insights that are complementary to those that can be obtained by experimental studies.

The first studied reaction is silica,  $\text{Si}(\text{OH})_4$  oligomerization, which is the basic step in zeolite synthesis. Zeolites are widely used in chemical industry due to the variety of different internal structures. Therefore, it is important to understand the earlier stages of their synthesis and how it is affected by different reaction conditions. The second studied reaction is ruthenium catalyzed transfer hydrogenation of ketones. In a transfer hydrogenation reaction, a double bond is reduced by a hydrogen donor, a catalyst usually facilitates the transfer of the hydrogens. The RuTsDPEN catalyst, developed by Noyori and coworkers, can catalyze this reaction with high enantioselectivity, up to 98% ee for several prochiral aromatic ketones. The efficiency of this catalyst is significantly improved in water solution, compared to organic solvents. Asymmetric transfer hydrogenation provides an effective route to chiral alcohols and is very useful for the pharmaceutical industry. Therefore, it is important to study the reactive process in more detail and understand how its efficiency is improved in presence of water.

## Methodology

Density functional theory, (DFT) was used to accurately describe bond breaking and formation during the reactions. The reactions in gas phase were studied by optimizing molecular geometries along the chosen reaction coordinates. For the reactions in solution, DFT was combined with molecular dynamics using Car-Parrinello molecular dynamics method. With this setup the thermal effects, due to numerous possible molecular configurations in solution were added. Rare event methods were used to enforce the reactive transitions in solution. For most of the studies the constrained dynamics method was used. In addition, transition path sampling, (TPS), method was used for the transfer hydrogenation reaction. The energy barriers were obtained employing transition state theory. For gas phase studies, the energies from static geometry optimizations were used for obtaining the energy barriers. For the studies in water solution, thermodynamic integration of the calculated constrained force along the reaction coordinate provided the free energy profiles.

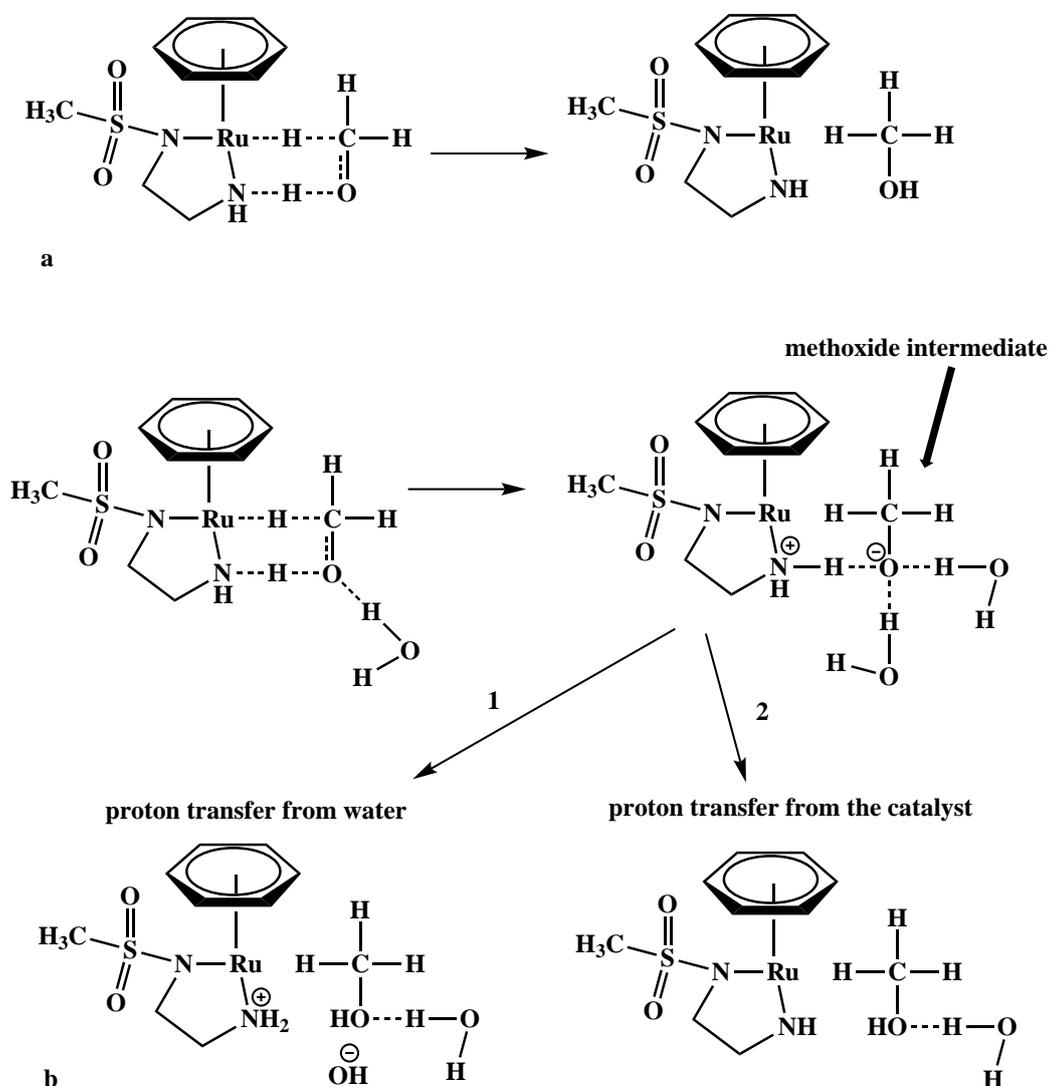
## Silica Oligomerization

In Chapter 2 the formation of silica dimers, trimers and 3-rings was studied in explicit water solution and in presence of a sodium ion. It was found that sodium increased the reaction barriers for all three cases, compared to the case with no ions present. However, the increase in reaction barriers was smaller than for lithium and ammonium ions, investigated in previous studies. Analysis of sodium's behavior showed that unlike the other ions, sodium was rarely in the first solvation shell of the reactive atoms. Instead, it was often in the second solvation shell, further away from the reacting atom, or coordinated to non reacting silica OH groups. Sodium is often seen to coordinate and decoordinate from OH groups of silica during the runs. However, these changes in coordination do not result in significant changes in the constrained force. Therefore, it was concluded that coordination to silica OH groups is not a likely reason for the increased reaction barriers. Correlation between sodium's distance to the reactive oxygen atoms in the first step of the reaction and the solvation of that atom was found. When sodium was in the first or second solvation shell of the oxygen, the average number of hydrogen bonds of that oxygen in water decreased. These observations illustrate how sodium could affect the hydrogen bond network of water, increasing the reaction barriers.

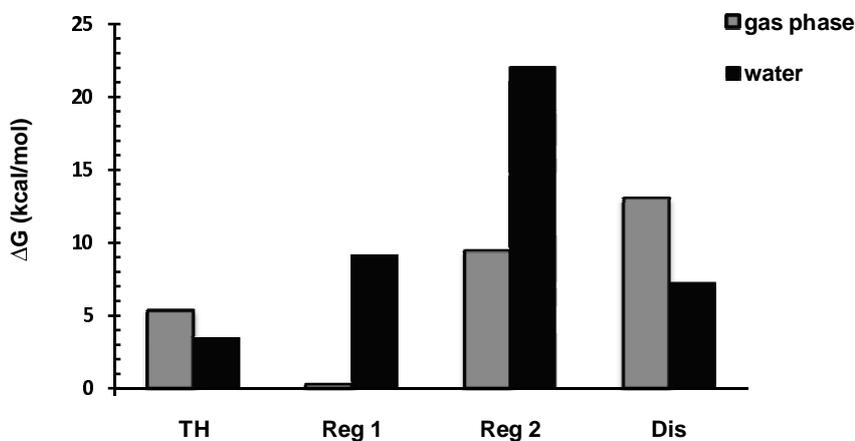
## Ruthenium Catalyzed Transfer Hydrogenation

Ruthenium catalyzed transfer hydrogenation of ketones is a cycle with two steps. The first step is transfer hydrogenation of the ketone by the catalyst. The second step is the regeneration of the catalyst by regaining the lost hydrogens from the donor substance. In Chapter 3, the transfer hydrogenation step was studied in water solution and compared to gas phase. Previous studies in gas phase showed that the two hydrogens were transferred simultaneously by the catalyst as a hydride and a proton. Specifically, the hydride was donated by the ruthenium atom, while the proton was donated by the  $\text{NH}_2$  moiety of the catalyst.

However, simulations in explicit water solution showed two differences. First of all, the reaction mechanism was sequential, with the hydride transfer preceding the proton transfer. Due to this, a methoxide intermediate stabilized by up to three hydrogen bonds from water molecules was observed. Secondly, the proton was transferred by a water molecule instead of the catalyst. This path in water had a lower reaction barrier than the simultaneous transfer of both hydrogens in gas phase, 3.5 kcal/mol and 5.7 kcal/mol, respectively. Since the catalyst remained protonated in water solution, its subsequent deprotonation was also studied. We found a deprotonation barrier of 18.6 kcal/mol in solution, which is marginally higher than previously calculated barriers for dissociation of water. This data could explain why a water molecule transferred the proton instead of the catalyst.



**Scheme 1:** a. The mechanism for transfer hydrogenation in gas phase. b. The two mechanisms for transfer hydrogenation in water solution.



**Figure 1:** Comparison of reaction barriers between water and solution for the studied steps in the reaction cycle of ruthenium catalyzed transfer hydrogenation of ketones. TH is the transfer hydrogenation step, Reg. 1 is regeneration of the protonated catalyst, Reg. 2 is regeneration of the deprotonated catalyst, Dis is dissociation of the ruthenium-formato complex.

In Chapter 4 the transfer hydrogenation step was studied in further detail with the TPS method. We confirmed that the reaction mechanism is sequential and showed that the methoxide intermediate could exist for over 1 ps. In addition, it was discovered that two mechanisms for the proton transfer are possible, both the catalyst and a water molecule could donate the proton. This is consistent with the deprotonation barriers for water and the catalyst being very close. Scheme 1 illustrates the difference between the mechanism in gas phase and the two different mechanisms in water. Analysis of selected reaction coordinates showed that two pathways with different proton transfer mechanisms can be very similar until this event. The simulations suggest that the proton transfer is decorrelated from the hydride transfer, and that random fluctuations decide if the methoxide receives the proton from water or the catalyst. In addition, the kinetic aspects of the reaction, not observed in constrained molecular dynamics simulations were revealed. In the hydride transfer step, the Ru-H bond was broken after the C-H bond was formed and the breaking could take up to 1 ps. The proton transfer was not observed before full breaking of this bond. Another important factor for the proton transfer was the formation of three strong hydrogen bonds, which occurred only after the hydride transfer. These structural changes could be the reasons for the sequential mechanism in solution.

The regeneration of the RuTsDPEN catalyst was studied in Chapter 5. The studied reactions were hydride transfer between the hydrogen donor, formate, and the catalyst with and without a proton. In this reaction the catalyst regains the hydride while formate is converted to carbon dioxide. Also the dissociation of the ruthenium-formato complex, observed experimentally in THF solvent, was studied. The reactions were simulated in both water solution and gas phase in order to understand the role of water. It was found that water increased the barrier for hydride transfer, but decreases the barrier for complex dissociation. These effects

could be explained by the strong hydrogen bonding between formate and water molecules. This hydrogen bonding disappears when formate is converted to carbon dioxide during the hydride transfer but increases when formate is dissociated from RuTsDPEN. Enthalpy contributions from those bonds could cause the differences in the reaction barriers between water and gas phase. Furthermore, the hydride transfer barrier was significantly higher for the deprotonated catalyst, and the catalyst was protonated by a water molecule in the process. Our simulations suggest this protonation is an important step in the cycle. In the reaction pathway observed in Chapter 3, the catalyst retains its proton and the protonation of the catalyst can be skipped. This could enhance the reaction rate of the whole transfer hydrogenation cycle.

This study of various reactions in the cycle of ruthenium catalyzed transfer hydrogenation of ketones illustrates how water can influence the separate parts of the cycle differently. The barriers for transfer hydrogenation and dissociation of ruthenium-formate complex are decreased, while the barrier for hydride transfer between the hydrogen donor and the catalyst is increased. In addition, aqueous solution provides a different mechanism in which a water molecule donates its proton to the ketone directly, instead of going through the catalyst's  $\text{NH}_2$  group. This pathway decreases the barrier for the regeneration of the catalyst. Figure 1 compares the studied reaction barriers between water and gas phase. The sum of all the influences of water solution is beneficial for the reaction, as confirmed by experiments.