Understanding the role of aqueous solution in chemical reactions: A computational study
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In this chapter reactions related to the regeneration part of RuTsDPEN-catalyzed transfer hydrogenation cycle have been studied. Specifically, hydride transfer between formate and a protonated and deprotonated catalyst and the dissociation of the ruthenium-formato complex have been studied. It was shown that water solution has a significant effect on the reaction barriers, increasing the hydride transfer barrier, while decreasing the complex dissociation barrier. These effects could be attributed to several hydrogen bonds between formate and water molecules, which favor the formate to be in solution. Furthermore, the hydride transfer barrier was significantly higher for the deprotonated catalyst, suggesting that the protonation state is important.\(^1\)

\(^1\) This chapter is to be published as "Mechanistic Aspects of Transfer Hydrogenation with Formate in Aqueous Solution" A. Pavlova, E. Rösler, E. J. Meijer
5-1 Introduction

Reduction of C=C, C=N or C=O bonds is an important transformation in chemistry. It is often done in a transfer hydrogenation reaction using a molecular hydrogen donor. Asymmetric transfer hydrogenation, ATH, of ketones is an easy route to chiral alcohols, and therefore, has many potential applications in pharmaceutical and fine chemical industries. One of well known catalyst for this reaction is the Noyori-Ikariya catalyst [1; 2], that uses p-cymene and TsDPEN (TsDPEN=N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine) ligands around a ruthenium atom, see Scheme 5.1. This catalyst was originally developed to be used with 2-propanol as the hydrogen donor and it can hydrogenate various prochiral ketones to alcohols with up to 98 % ee [1].

The choice of the solvent and the hydrogen donor has a significant effect on the yield, selectivity and the reaction rate of ATH. While using 2-propanol as the hydrogen donor and the solvent gives good reaction rates, the reaction is also reversible [2; 3]. Due to this, the conversion is not fully completed and the enantiopurity of the product deteriorates with time. The yield and the enantioselectivity improves significantly when formic acid/triethylamine mixture is used as both the hydrogen donor and the solvent [3]. However, the reaction rate is too slow to be feasible [3]. Recently, Xiao and coworkers discovered that the rate and the yield of ATH with the Noyori-Ikariya catalyst increases significantly in water solution with NaCOOH and water as hydrogen donors, with only a slight loss of enantioselectivity [4–6]. They also measured a secondary kinetic isotope effect for water, suggesting that it is involved in the limiting reaction step [7]. However, a full mechanistic understanding of how water increases the reaction rate in this reaction is still lacking. Since water is a green, cheap and safe solvent that is also essential for mimicking biocatalytic mechanisms, it is of general importance to understand catalytic processes in aqueous solution. In addition, formic acid and its base, formate, are commonly used in chemical industry as hydrogen donors. Therefore, it is important to understand their role in the transfer hydrogenation cycle and how their reactivity is influenced by solution.

Several experimental [1; 7–12] and theoretical [7; 9; 13–16] studies have investigated

\[ \text{Scheme 5.1: The Noyori-Ikariya catalyst for ATH. 1. The 18 electron ruthenium complex that hydrogenates the ketone. 2a. The resulting 16 electron ruthenium complex after the transfer hydrogenation step. 2b. The resulting 16 electron ruthenium complex theoretically observed in water solution.} \]
the mechanism of ruthenium catalyzed ATH. It has been concluded that an 18-electron ruthenium hydride complex, 1, displayed in Scheme 5.1 is formed and that this complex transfers the hydride to the ketone. Therefore, the ATH reaction cycle must have at least two steps. The transfer hydrogenation step, where the two hydrogens are transferred to the substrate, and the regeneration step where the dehydrogenated 16-electron ruthenium catalyst 2a or 2b, shown in Scheme 5.1, must regain its hydride in order to be active, see Scheme 5.2.

The catalyst regeneration is the limiting step in ATH with 2-propanol [9; 13–16], while in formic acid/triethylamine mixture the reaction rates of transfer hydrogenation and regeneration steps are close to each other [11]. In water solution, the reaction appears to be of first order in the catalyst, formate and the ketone at low concentrations of the mentioned substances. However, this behavior is not observed at higher concentrations of formate and the ketone [4; 7; 12]. Therefore, it is still unclear what is the rate limiting step of this reaction in water. Identifying the limiting step of aqueous ATH would facilitate its further improvement.

The transfer hydrogenation step has been studied in gas phase [9; 13–15] and in explicit methanol [16] and water solutions [17]. The studies in gas phase and methanol solution showed that both of the hydrogens in the transfer hydrogenation step are provided by the catalyst, resulting in the formation of 2a. This is also supported by the crystal structure studies of the catalyst in 2-propanol [8]. However, when significant solvent effects are present, using an explicit solvent model can be important, as exemplified by several previous studies [16–27]. For example, a study of a similar ruthenium catalyst in explicit methanol solution showed a decreased reaction barrier and a possible mediation of the proton transfer

\[
\text{Scheme 5.2: The cycle of Ru-catalyzed ATH of ketones. D=Hydrogen Donor. a. Non aqueous solvents, X=NH, m=2. b. Aqueous solution X=NH}_2^+, m=1.\]
Regeneration of RuTsDPEN in Transfer Hydrogenation

from a solvent molecule [16]. Furthermore, our recent study of the transfer hydrogenation step of ATH in explicit water solution [17] showed that a water molecule transfers a proton to the ketone instead of the catalyst. In this case, the catalyst, remains protonated and 2b is formed instead of 2a, see Scheme 5.2. Note, 2b only needs to receive a hydride for continued activity. Scheme 5.2 illustrates the difference between ATH in water and other solvents.

The regeneration step has been less studied than the transfer hydrogenation step for formic acid or formate as hydrogen donors. Koike et al. studied this reaction in THF solvent [10] and proposed the mechanism shown in Scheme 5.3 based on the detection of ruthenium-formato complex, 3, that eventually forms 1. There are two possible pathways from 3 to 1, decoordination of formic acid, followed by a direct hydride transfer, or migration insertion mechanism [10] see paths A and B, respectively, in Scheme 5.4. Note that path B in the case of this catalyst would require decoordination of the aromatic ligand [9; 13–15], making it highly unfavorable.

Here we investigate how our previous fundings for the transfer hydrogenation step [17] affect the regeneration of the Noyori-Ikaria catalyst. Furthermore, since formic acid and formate can have strong favorable interactions with water molecules [28–30], we also studied how water solution influences the reactivity of formate in transfer hydrogenation. Based on previous gas phase studies, that show high barriers for migration insertion mechanism in the case of RuTsDPEN, we only considered path A in our study. We report an ab initio molecular dynamics study of direct hydride transfer from formic acid to the ruthenium catalysts 2a and 2b and the dissociation of ruthenium-formato complex, 3, in explicit aqueous solution.

5-2 Methods

Due to the high costs of density functional theory, DFT, a simplified model of the catalyst, shown in Scheme 5.5a, was used. We replaced the cymene ligand with a benzene ligand, and the TsDPEN ligand with a 1,amino-2,methylsulfonamide-ethane ligand. In this model the electronic structure around the ruthenium atom remains the same as in the original catalyst. The system consisted of the model catalyst and formate dissolved in a periodic,
body centered cubic, bcc, box with 54 water molecules. The same models of the catalyst and the solvent were used in our previous study.

We used the Kohn-Sham formulation [31] of DFT [32] to describe the electronic structure. We chose the BLYP density functional [33; 34], that uses the exchange term proposed by Becke [33] and the correlation term proposed by Yang, Lee and Par [34]. It describes with an acceptable accuracy the properties of water [35; 36] and ruthenium catalyzed transfer hydrogenation [15]. A plane-wave basis set that included waves up to 70 Ry was used to expand the Kohn-Sham orbitals. The non-valence electrons were described with Troullier-Martìn pseudopotentials [37; 38]. The ruthenium pseudopotential was of the semi-core type including the highest s-, p- and d-shell electrons as valence electrons. The pseudopotential cut-off radii for s, p and d terms were 1.10, 1.20, 1.24 a.u., respectively. The pseudopotential cut-off radii for S, C, N, O and H were 1.34, 1.23, 1.12, 1.10, and 0.50 a.u., respectively, for the s terms. The pseudopotentials for S, C, N and O also used the same cutoff for the p term as for the s term. An additional d term with a cutoff of 1.34 was added for the sulfur atom. We used the CPMD program package for all of the calculations described here [39].

The reaction in water was studied with Car-Parrinello molecular dynamics [40]. In this ab initio molecular dynamics method the coefficients of the plane wave basis set are given

**Scheme 5.4:** Possible paths A and B for transfer of hydride to the ruthenium atom in the ruthenium-formato complex.
a fictitious mass and are propagated dynamically. The electronic structure remains near the ground state, provided that the fictitious mass is sufficiently small. The fictitious mass was 600 a.u. and the time step was 0.12 fs in our simulations. We assigned a deuterium mass to the hydrogen atoms in order to use a larger time step. This simulation setup provides a sufficiently accurate description of water [36]. The molecular dynamics were done at a constant volume and temperature. We used a Nosé-Hoover thermostat [41; 42] with a frequency of 500 cm\(^{-1}\) to keep the temperature at a target value of 350 K. The cell volume was 2.0 nm\(^3\) based on the crystal volume of the catalyst [8] and the densities of water and formic acid.

\[
\Delta G = -\int_{r_1}^{r_2} \langle F(r) \rangle dr \quad (5.1)
\]

Since chemical reactions occur on a time scale that is presently not accessible by ab initio molecular dynamics simulations, we used the constrained dynamics method [43] to simulate the reactions and obtain the free energy profiles. In this method, a reaction coordinate, \(Q\), is chosen and the molecular dynamics simulations are done at several fixed values of this coordinate. The average constrained force that is needed to keep the constraint at the given value is measured and can be used to calculate the free energy profile according to Eq 5.1. In this equation, \(F\) is the average constrained force and \(r\) is the value of the reaction coordinate. For each measured constraint value we performed a 2 ps equilibration simulation, followed by a 10 ps sampling simulation, the latter was used to calculate the average constrained force. In order to investigate the hysteresis effect we did this procedure starting from both the reactant and the product state. For the dissociation of the ruthenium-formato complex, we used the Ru-O distance as the reaction coordinate, see Scheme 5.5b. For the hydride transfer reaction we used the asymmetric stretch Ru-H-C, that is the difference between the Ru-H distance and the C-H distance, as shown in Scheme 5.5c.

For the studies in gas phase, we used the same density functional, basis set, pseudopotentials and program package as for the studies in solution. An isolated cubic cell with a volume of 8.0 nm\(^3\) was used. The energy profiles were obtained by constrained geometry optimizations along the same reaction coordinates as in solution. Zero points energies
were not added, as the energy profiles in gas phase were only used to clarify the differences between gas phase and solution.

5-3 Results and Discussion

5-3.1 Dissociation of the Ruthenium-Formato Complex

The average constrained force was sampled between Q values of 2.19 and 3.05 Å and was close to 0 at those points. The force profiles in solution are displayed in Figure 5.1a, while the free energy profiles of the reaction in solution are compared to gas phase energies in

![Figure 5.1](image)

**Figure 5.1:** a. Constrained force profiles for backward and forward reactions in the intermediate dissociation. The statistical errors are calculated as in 95 % confidence interval. b. The corresponding free energies, gas phase energies are added for comparison.
Figure 5.2:  

a. Comparison of the average distance between the closest formate oxygen and the NH$_2$ group of catalyst in water to gas phase geometries.  
b. The average number of hydrogen bonds for the two formate oxygens during the reaction.  
O1 is the oxygen in the Ru-O bond and O2 is the oxygen that is initially bound to the NH$_2$ moiety of the catalyst.  
Only the hydrogen bonds shorter than 2.2 Å were counted.  
The statistical errors are less than 0.4.

Figure 5.1b.  
There is no barrier for the formation of this complex, which is consistent with experimental studies[10; 11], that showed very fast formation rate.  
There is some hysteresis in the constrained force, however it results in very small differences for the free energy barriers.  
The reaction barrier was 7.2 kcal/mol in water solution, while in gas phase it was substantially higher, 13.0 kcal/mol.  
These energy barriers discrepancies could be attributed to the water molecules that stabilize the negative charge of the formate with hydrogen bonds during and after the dissociation.  
In gas phase, formate can only form a hydrogen with the NH$_2$ moiety of the ruthenium catalyst, while in solution it can form several hydrogen bonds.
Figure 5.3: Selected snapshots from the formation of the ruthenium-formato complex, important bond distances are shown in Å. The formate oxygens are enlarged and colored purple for clarity. Q=2.19 Å. The stable ruthenium-formato complex. The formate oxygen bound to the ruthenium atom does not have any hydrogen bonds, the other formate oxygen has a bond with water and a bond with the NH$_2$ group of the catalyst. Q=2.65 Å. At this point in the dissociation process the formate-catalyst hydrogen bond is seen to break and reform, it is broken in this snapshot. The hydrogen bonding between formate and water is increased compared to the stable complex. Q=2.95 Å. The ruthenium oxygen bond is broken and this oxygen is hydrogen bonded to the amino group of the catalyst instead. Formate has four hydrogen bonds in total now, three with water molecules and one with the catalyst.

Another interesting difference between gas phase and solution is the change in the hydrogen bond between the non-reactive oxygen of formate, O1, and the NH$_2$ moiety of the catalyst, displayed in Figure 5.2a. In gas phase, this bond is becoming shorter during the dissociation, while in solution it is starting to break at Q=2.95 Å and is broken completely when Q=3.05 Å. This suggest that the NH$_2$ moiety of the ruthenium catalyst plays a less important role in this reaction in solution, where solvent molecules can also provide hydrogen bonds. Figure 5.3 shows selective snapshots during the reaction, where the changes in the hydrogen bonding mentioned above are illustrated.

The backward barrier in solution was 6.7 kcal/mol, considering that DFT gives an error of 1-2 kcal/mol, this is not significantly different from the forward barrier. There are some differences in the hydrogen bonding of formate for forward and backward reactions. In the backward reaction, there is less difference in the hydrogen bonding of the two formate oxygens. In addition, the hydrogen bond between the formate and the NH$_2$ moiety of the catalyst is longer and more stable than in the forward case. These structural differences could explain the small hysteresis.
Figure 5.4: a. The constrained force profiles for the backward and forward reaction for hydride transfer between formate and the protonated catalyst. The statistical errors are calculated as in 95% confidence interval. b. The corresponding free energies in solution.

Note, that in aqueous ATH, the formation of this complex is not needed for the regeneration of the catalyst and therefore it is not necessary an intermediate. Instead, due to no barrier of formation and a significant barrier for dissociation for complex 3, formate could also act as an inhibitor of the catalyst. That could explain the non linear reaction kinetics at different concentrations of formate [4; 7; 12]. The reduction of the dissociation barrier for this complex could be one of the reasons for the increased reaction speed of the whole ATH cycle in water.
5-3 Results and Discussion

5-3.2 Hydride Transfer to the Protonated Catalyst

The reaction coordinate Q was sampled between values of -1.44 and 2.36 Å. The average constrained forces are shown in Figure 5.4a, and the free energy profiles in solution in Figure 5.4b. The reaction appears to be barrier-less in gas phase. In fact, an unconstrained geometry optimization of the reactants ends up in the product state. This could be due to the charge separation in the reactants that evens out during the reaction. Similar energetic results were obtained by Matsubara [44], when studying the reverse reaction with another

![Graphs showing O-NH₂ bond lengths and hydrogen bond counts](image)

**Figure 5.5:** a. Comparison of the average distance between the closest formate oxygen and the NH₂ group of catalyst in water to gas phase geometries. b. The average number of hydrogen bonds for the two formate oxygens during the reaction, O₁ is the oxygen that is forming the NH₂ bond. Only the hydrogen bonds shorter than 2.2 Å were counted. The statistical errors are less than 0.4.
Surprisingly, we obtained a significant barrier for this reaction in water solution. Due to the small hysteresis in the force profiles, there is also a small difference between forward and backward reaction barriers. The forward barrier was 9.1 kcal/mol, whereas the backward barrier was 10.3 kcal/mol, this difference is within the errors expected from DFT.

Evidently, aqueous solvent significantly decreases the reaction rate of hydride transfer from formate to the ruthenium catalyst. Again, this effect can be attributed to waters remarkable ability to form hydrogen bonds. Before the reaction, both of the formate’s oxygens have several hydrogen bonds with water molecules or the catalyst, as displayed in Figure 5.5b. However, the product, carbon dioxide, has a limited ability for form hydrogen bonds. As Figure 5.5b shows, the number of hydrogens bonds for the reactants oxygens is decreasing during the reaction until it becomes almost 0 at the transition state, where the constrained force changes sign. The cost of breaking those hydrogen bonds could be the reason for the significantly increased reaction barrier. Figure 5.6 shows selected snapshots from the reaction, illustrating the dramatic changes in hydrogen bonding of the substrate. The hydrogen bond between the NH$_2$ moiety of the catalyst and formate is around 2.0 Å long in the beginning and is slowly broken during the reaction, see Figure 5.5a. There are significant fluctuations in this distance in solution, which is not observed in the complex dissociation. These fluctuations could explain the small hysteresis in the force between the forward and the backward reaction. Another possible reason for the hysteresis is the slower formation of the first hydrogen bonds between water and formate in the backward reaction, compared to the abrupt breaking of these bonds in the forward reaction, see Figure 5.5b.

**Figure 5.6:** Selected snapshots from the hydride transfer reaction to the protonated ruthenium catalyst, important bond distances are displayed in Å. The formate oxygens and the transferred hydride are enlarged and darker colored for clarity. Q=1.96. The hydride is far away from the ruthenium atom and the formate has several strong hydrogen bonds with water. There is no hydrogen bond between formate and the catalyst. Q=0.75, as the distance between the hydride ruthenium decreases, a hydrogen bond is formed between one of the formate oxygens and the catalyst. In addition, the number of the hydrogen bonds and their strength is starting to decrease. Q=0.25. Around the transition state, the substrate has almost no hydrogen bonds anymore.
5-3.3 Hydride Transfer to the Deprotonated Catalyst

We investigated the difference between the protonated and the deprotonated catalyst in the hydride transfer reaction. The constrained force was measured for Q values between -1.23 and 2.36 Å. Figure 5.7a and Figure 5.7b show the force and the free energy profiles, respectively. The reaction barrier is significantly increased in both gas phase and solution compared to the protonated catalyst. In gas phase, instead of a barrier-less reaction, we see a barrier of 9.4 kcal/mol, while in solution the barrier is increased from 9.1 kcal/mol to 22.0 kcal/mol. In addition, a water molecule protonates the catalyst in solution at Q=0.38

![Graph](image)

**Figure 5.7:** a. The constrained force profiles for the backward and forward reaction for hydride transfer between formate and the deprotonated catalyst. The statistical errors are calculated as in 95% confidence interval. b. The corresponding free energies, gas phase energies are added for comparison.
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Figure 5.8: The average number of hydrogen bonds for the two formate oxygens during the hydride transfer from formate to the deprotonated catalyst. O1 is the oxygen that is closest to the NH group. The statistical errors are less than 0.4 Å, just before the transition state. Due to this event, the hysteresis effect could only be investigated from Q=0.38Å. There are some differences in the constrained forces close to this point because of frequent proton transfers between a water molecule and the catalyst. Eventually, at Q=0.97, these transfers stops, the constrained forces become very close for the two profiles and the resulting free energy curves are very close as well.

Figure 5.9: Selected snapshots from the hydride transfer reaction to the deprotonated ruthenium catalyst. The formate oxygens and the transferred hydride and proton are enlarged and colored differently for clarity. The formate oxygens are purple, while the hydride and the proton are dark gray. Q=1.96. The beginning of the reaction, the solvation of formate is very similar to the protonated case. Q=0.35. A proton is transferred to the NH to group of the catalyst at this stage, resulting in a hydrogen bond between formate and the catalyst. The total hydrogen bonding of formate is significantly decreased, just as in the protonated case. Q=0.14. Around the transition state, just as in the protonated case, formate has almost no hydrogen bonds anymore.
The difference in the reaction barriers between the two catalysts suggest that the protonation of the NH moiety of the catalyst is an important step in ATH that needs to happen before the hydride transfer. Therefore, the slightly different pathway for the transfer hydrogenation in water [17], where the catalyst remains protonated, could increase the reaction rate of the whole ATH cycle. The hydrogen bonding of the formate oxygens, shown in Figure 5.8 looks almost the same as in the protonated case. Consequently, the difference in the reaction barriers between aqueous solution and gas phase could again be attributed to the breaking of hydrogen bonds between formate and water during the reaction. The NH group is less prone to hydrogen bonding than the NH$_2$ group. Due to this, hydrogen bonding between the catalyst and formate is not observed until the NH group is protonated, as shown in the selected snapshots in Figure 5.9.

5-4 Discussion and Conclusions

We have studied reactions relevant to the regeneration of the 16 electron RuTsDPEN complex in aqueous solution, using an explicit solvent model. Specifically, we studied the dissociation of the ruthenium-formato complex, first discovered by Koike et al.[10] and the hydride transfer from formate to the ruthenium catalyst. The latter reaction was studied for both the protonated and the deprotonated catalyst, in order to investigate the effect of the proton.

For the dissociation of the ruthenium-formato complex it was found that water decreases the barrier of dissociation by 6 kcal/mol. This could be attributed to several hydrogen bonds between formate and water molecules during the reaction, that stabilize the formate. In both gas phase and solution studies there was no barrier for the formation of this complex, which is consistent with experimental studies[10; 11]. Due to the low formation barrier and the high dissociation barrier, the formation of this observed complex could inhibit the ruthenium catalyst. Since water solution increases the dissociation rate of the ruthenium-formato complex, it could be one of the reasons for the increased reaction rate in aqueous ATH.

For the hydride transfer from formate to the ruthenium catalyst, we found that aqueous solvent increases the reaction barrier for both protonated and deprotonated catalysts. Again, this could be caused by several hydrogen bonds between formate and solvent molecules that make formate more stable in water solution. This energetic stabilization of the reactant could increase the energy barrier for the hydride transfer since the product, carbon dioxide, does not form hydrogen bonds. Both in gas phase and in solution, the reaction barrier was significantly increased for the deprotonated catalyst. In addition, a water molecule protonated the deprotonated catalyst in solution before the transition state. Based on our results, protonation the NH moiety of the catalyst is an important step that needs to happen before the hydride transfer from formic acid.

A summarized energy diagram is shown in Figure 5.10. The total barrier of going from the ruthenium-formato complex, to ruthenium 18 electron complex, 1, and carbon dioxide is 13.1 kcal/mol in gas phase, and 16.3 kcal/mol in water. Our simulations suggest
that water increases the reaction barrier for the regeneration step in transfer hydrogenation with RuTsDPEN. On the other hand, the formation of the ruthenium-formato complex is not necessary in aqueous solution, and could inhibit the catalyst. Therefore, the lowering of the dissociation barrier for this complex could compensate for the increased barrier of the hydride transfer. Thus, the total effect of water on this reaction step could still be beneficial. Further kinetic and theoretical studies are needed in order to clarify the role of the ruthenium-formato complex in aqueous ATH.

Our result illustrate the complexity of solvent effects on a reaction cycle with several steps and the need of incorporating solvent effects when investigating aqueous chemistry. Furthermore, this study illustrates the different reactivity of formate in water compared to an environment without hydrogen bonds.

5-5 References


5-5 References


