Understanding the role of aqueous solution in chemical reactions: A computational study

Pavlova, A.

Citation for published version (APA):
In this chapter, the transfer hydrogenation of ketones with RuTsDPEN in water was studied with transition path sampling. Two different mechanisms for the proton transfer part of the reaction were found. The proton could be transferred to the ketone by either a water molecule or the catalyst. Furthermore, analysis of the reaction coordinates showed that two structural changes occur between the hydride transfer and the proton transfer. The hydride moves further away from the ruthenium and the carbonyl oxygen forms three strong hydrogen bonds with either water molecules or the catalyst. This could explain why the transfer hydrogenation mechanism is sequential in aqueous solution in contrast to gas phase.
4-1 Introduction

Hydrogenation of C=O double bonds is an important transformation in chemistry. In a transfer hydrogenation reaction this is done by using a hydrogen donor and a catalyst that facilitates the transfer of a hydride and a proton from the donor to the ketone. Efficient asymmetric transfer hydrogenation, ATH, of ketones is an effective route to optically active alcohols and is highly desirable in the pharmaceutical industry. The development of catalysts with significant efficiency for the ATH reaction started two decades ago. Noyori and coworkers have developed several ruthenium based catalysts [1–4]. Their RuTsDPEN catalyst, displayed in Scheme 4.1a, has been shown to give high enantioselectivity, up to 98 % ee for a large range of substrates [2]. The choice of solvent and hydrogen donor is important for the reaction rates and enantioselectivity in transfer hydrogenation with ruthenium based catalysts [2–8]. In the initial reaction setup 2-propanol was used as both the hydrogen donor and the solvent. It resulted in high reaction rates, however, as the reaction is reversible, full conversion could not be achieved [2–5]. The yield and the enantioselectivity are improved if formic acid/triethylamine mixture is used as both the solvent and the hydrogen donor, however at the price of a slower reaction rate [3; 5]. This issue can be solved if formate is used as the hydrogen donor in aqueous solution. As shown by Xiao and coworkers [6–8], the efficiency and the reaction rate of the catalyst are significantly improved, while the high enantioselectivity is maintained. Compared to organic solvents, water is an environmentally friendly, cheap and safe option. Therefore, it is important to understand how aqueous solvent accelerates asymmetric transfer hydrogenation of ketones.

Several experimental [2; 9–14] and theoretical [10; 12; 15–19] studies have investigated the mechanistic aspects of transfer hydrogenation of ketones with RuTsDPEN and similar catalysts. Experiments in organic solvents and gas phase studies concluded that the reaction occurs via metal ligand bifunctional mechanism, see Scheme 4.1b [2; 9; 10; 12; 15–18]. In this mechanism, the catalyst first receives the two hydrogens from the donor and then transfers both of those hydrogens to the ketone simultaneously, Scheme 4.2 shows the full reaction cycle [2; 9; 10; 15–17]. The hydrogens are transferred to the ketone as a hydride.
and a proton and the NH₂ moiety of the catalyst is attributed a crucial role, since it transfers the proton [2; 9; 10; 12; 15–18]. However, if solvent effects play an important role, theoretical gas phase studies may not always provide the full mechanistic details. Experiments strongly suggest that water molecule participates in the rate limiting step due to secondary kinetic isotope [12]. Also, previous theoretical studies in explicit methanol [18] and water solutions [19] showed a more complex picture in which solvent molecules can directly participate in the reaction. The study in water solution showed a two step mechanism, where only the hydride is transferred in the first step, followed by a transient appearance of a methoxide intermediate. In the second step, a water molecule transferred a proton to the ketone instead of the catalyst [19], see Scheme 4.3. Note, in this mechanism the catalyst remains protonated and only needs to receive a hydride from the hydrogen donor. Our study of the hydride transfer between formate and RuTsDPEN, described in Chapter 5, showed that the catalyst has to be protonated before the transfer can proceed. Thus, the elimination of catalyst deprotonation and protonation could be the reason for increased reaction rate in water.

In view of our previous results we decided to study ruthenium catalyzed transfer hydrogenation in water in more detail in order to further elucidate the role of the solution. The previous study used constrained dynamics with the Ru-H-C asymmetric stretch as the reaction coordinate to enforce the reaction [19]. Transition path sampling, TPS, used here, is a method for studying reactive transitions that does not depend on a reaction coordinate. In addition, no artificial dynamics are introduced and real kinetic pathways for transitions between two states [20; 21] are obtained. Due to this, TPS can be used to calculated the reaction rates with a higher accuracy than transition state theory. Unfortunately, a large

![Scheme 4.2: The cycle of Ru-catalyzed ATH of ketones. D=Hydrogen Donor. a. Non aqueous solvents, X=NH₂, m=2. b. Aqueous solution X=NH⁺, m=1.](image)
Scheme 4.3: An alternative mechanism for ATH with RuTsDPEN observed in water solution. In the first step only the hydride is transferred and a methoxide intermediate stabilized by up to three water molecules is formed. In the second step, a water molecule transfers a proton to the ketone while the NH₂ moiety of the catalyst is never deprotonated.

amount of reactive trajectories is needed for calculations of reaction rates, therefore, it is not feasible for the large quantum chemical modeled system, studied here. Nevertheless, previous ab initio TPS studies provided more details about the investigated reactions. Many studies revealed different mechanisms, not seen with methods that require a reaction coordinate [22–26]. Geissler et al. showed that autoionization of water is initiated by electrostatic fluctuations and that the transition state for the reaction is the breaking of the hydrogen bond network between the formed hydroxide and hydronium ions [22]. Parks et al. studied deprotonation of acetic acid and found two slightly different reaction mechanisms; the reaction could start with the proton transfer followed by rearrangement of the solvent, or the other way around [24]. Ensing et al. studied the Fenton reagent reaction, Fe²⁺ + H₂O₂ → [FeIV O]²⁺ + H₂O and found two different mechanisms for hydrogen shuttling to the formed hydroxyl radical intermediate, either directly from the iron ligand or via the hydrogen bond network of water [23]. Finally, dehydrogenation and cracking of propene in zeolites has been studied [25; 26]. In the former case it was found that entropic contributions are important for the reaction barriers, while the latter study showed two slightly different mechanisms for the C-C bond dissociation.

Transfer hydrogenation reactions have not been previously studied with TPS. Here we present an ab initio transition path sampling study of a transfer hydrogenation of formaldehyde with a model RuTsDPEN catalyst in explicit aqueous solution.
4-2 Methods

In view of the high computational costs of density functional theory, DFT, and in order to be consistent with our previous study, we used simplified versions of the catalyst and the reactant [19]. Formaldehyde was used as the reactant and the model catalyst is shown in Scheme 4.4a. The cymene and the TsDPEN ligands of the catalyst were replaced with benzene and 1-amino-2,methylsulfonamide-ethane, respectively. The electronic structure around the ruthenium atom remained the same as in the original catalyst. The aqueous solvent was represented by 54 water molecules in a periodic body centered cubic, bcc, cell.

![Scheme 4.4:](image)

**Scheme 4.4:** a. The model catalyst used in our simulations. b. The definition of state A, the formaldehyde state. c. The definition of state B, methanol that is not hydrogen bonded to a hydroxide.

The electronic structure was calculated using the Kohn-Sham formulation [27] of DFT [28]. The BLYP density functional that employs the Becke [29] exchange term and the LYP correlation term [30], was used because of its sufficiently accurate description of both water [31; 32] and ruthenium catalyzed transfer hydrogenation [17]. We used a plane-wave basis set that included waves up to 70 Ry to represent the Kohn-Sham orbitals. Troullier-Martín pseudopotentials [33; 34] were used to account for interaction of the valence electrons with the core electrons. The pseudopotential cut-off radii for the s term for S, C, N, O and H atoms were 1.34, 1.23, 1.12, 1.10 and 0.5 a.u., respectively. For S, C, N and O atoms the same cutoff was also used for the p term. For the sulfur atom an additional d term with a cutoff of 1.34 a.u. was added. The ruthenium pseudopotential was of the semi-core type and included 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 and 1.24 a.u., respectively.

The ab initio molecular dynamics simulations were done using the Car-Parrinello method [35] and the CPMD program package [36]. In this method, the wavefunction coefficients are given a fictitious mass and are propagated dynamically together with the nuclei. The electronic structure remains close to the ground state, provided that the fictitious mass is sufficiently small. Deuterium was used instead of hydrogen to allow for a larger time step. The fictitious mass was 600 a.u., which allowed to use a time step of 0.12 fs. This simulation setup provides a sufficiently accurate description of water [32]. The simulations were done in the NVT ensemble. The temperature was kept at the target value of 350 K using a Nosé-Hoover thermostat [37; 38] with a frequency of 500 cm$^{-1}$. The periodic cell volume was 2.0 nm$^3$, based on the densities of the catalyst [9], water and formaldehyde.
Reactive Path Sampling of Transfer Hydrogenation.

Figure 4.1: An example of generating new trajectories from an existing one with shooting moves. A phase space point $x^o_i$ is randomly chosen from the path, and its momentum, $p^o_i$, is slightly modified to new momentum, $p^n_i$. The path is then integrated backward and forward in time, using the new momentum. Attempt 1 is rejected since it does not end in B, while Attempt 2 is accepted since it connects the two states.

The TPS method, employed here, generates reactive trajectories with a probability that is proportional to their weight in the transition path ensemble [20; 21]. It uses a markov chain monte carlo, MCMC, scheme [39] to generate a new trajectory from the existing one. While TPS does not require a reaction coordinate, the correct definition of stable states A and B, between which the transition occurs is needed [20; 21].

A trajectory of k steps, $\tau(x)$ can be is discretized as in Eq. 4.1, where $x_i$ represents the phase-space point, (the coordinates and the momentum of all particles in the system), at time i. Since we are only interested in reactive trajectories, terms $h_A[x_0]$, $h_B[x_k]$, and reactive path probability, $P_{AB}[\tau(x)]$, are introduced. $h_A[x_0] = 1$ if $x_0$ is in region A and zero otherwise, while $h_B[x_k] = 1$ if $x_k$ is in region B and zero otherwise. $P_{AB}[\tau(x)]$ is defined as in Eq. 4.2, where $P[\tau(x)]$ is the probability of the path $\tau(x)$.

$$\tau(x) = \{x_0, x_1, \ldots, x_i, \ldots, x_k\}$$  \hspace{1cm} (4.1)

$$P_{AB}[\tau(x)] = h_A[x_0]h_B[x_k]P[\tau(x)]$$  \hspace{1cm} (4.2)

There are several approaches, "moves", to generate a new trajectory from the old one. If the new trajectory does not start in A or does not end in B, it is rejected and the old trajectory is counted in the ensemble average. Otherwise, it is accepted with its statistic probability and is used for the generation of the next pathway. The acceptance probability is calculated from the detailed balance criteria in Eq. 4.3 from MCMC. $\tau^o(x)$ is the old path, while $\tau^n(x)$ is the new path. $P_{acc}[(\tau(x))]$ is the acceptance probability of $\tau(x)$, $P[\tau(x)]$ is the probability of $\tau(x)$ and $P_{gen}[\tau^n(x) \rightarrow \tau^o(x)]$ is the probability to generate $\tau^n(x)$ from $\tau^o(x)$ [20; 21]. The exact acceptance criteria can be derived depending on which move is made.

$$\frac{P_{acc}[(\tau^o(x) \rightarrow \tau^n(x))]}{P_{acc}[(\tau^n(x) \rightarrow \tau^o(x))]} = \frac{P_{AB}[\tau^n(x)]P_{gen}[\tau^n(x) \rightarrow \tau^o(x)]}{P_{AB}[\tau^o(x)]P_{gen}[\tau^o(x) \rightarrow \tau^n(x)]}$$  \hspace{1cm} (4.3)
We only used shooting moves in our simulations. In a shooting move a random phase-space point, \( x_i \), is picked from the trajectory and the momentum of all or some of the particles is slightly changed. A new trajectory is generated by integration both backward in time for \( i-1 \) steps and forward in time for \( k-i \) steps, so that the new trajectory is of the same length as the previous one. Since \( P_{gen}[\tau^n(x) \rightarrow \tau^o(x)] \) is equal to the probability to generate \( x^n_i \) from \( x^o_i \) in deterministic dynamics [20; 21], the acceptance criteria for a symmetric shifting move is shown in Eq 4.4, where \( \rho(x_i) \) is the probability of phase-space point \( x_i \).

\[
P_{acc}[\tau^n(x)] = \min \left[ 1, h_A[x^n_0]h_B[x^n_k] \frac{\rho(x^n_i)}{\rho(x^o_i)} \right]
\]

Correct definition of stable states A and B is important for an efficient and accurate TPS simulation. Based on our constrained dynamics study, the formaldehyde state, A, was defined as the phase-space region with configurations that have a Ru-H distance larger than 3.0 Å. For these configurations the average constrained force was close to 0 [19]. In addition, previous simulations in water showed quick proton transfers between solvent and the reactant [19]. Therefore, our definition of the stable methanol state included proton transfer to the carbonyl carbon and migration of the hydroxide from the first solvation shell of the formed methanol. The two stable states are also shown in Scheme 4.4b and c.

Trajectories of constant length were generated using shooting moves in which the momentum of each atom was rotated by maximally 2 degrees around either x, y, or z axis. The maximum displacement was chosen such that the acceptance rate would be at least 20 %, while distinct pathways could still be obtained. The magnitude of the rotation was set independently for each atom by generating a random number in the interval of [0,1] and scaling the value with the maximum rotation angle. The axis for rotation was also decided by a random number for each atom and the rotation was implemented using a rotation matrix. In this setup, the total value of the momentum and the total energy were conserved and a path was accepted if it started in state A and ended in state B. Storing wavefunction coefficients at every molecular dynamics time step would take a prohibitive amount of storage. Therefore, the full state of the configurations was saved every 625 steps, which corresponded to 7.6 fs intervals. In the TPS scheme, one of these configurations was randomly picked for a shooting move. At a shooting point, the coordinates, the wave function, the fictitious electronic velocities and the thermostat parameters were restarted. The backward integration was done using a negative timestep in the CPMD program. The reversibility of this setup was tested by integrating one of the obtained trajectories forward and backward and calculating the displacement of the most important atoms, the hydride and the carbonyl oxygen. Figure 4.2 shows that the forward and the backward trajectories are identical.
4-3 Results and Discussion

4-3.1 Transition Path Sampling Simulations

The initial path was generated by taking configurations from the constrained dynamics simulation close to the transition state, generating random velocities and integrating forward and backward until a path passing the states A and B was found. Surprisingly, the catalyst and not a water molecule transferred the proton to the formaldehyde in the initial path. This has not been observed in the constrained molecular dynamics simulations. Several shooting moves combined with manual shifting of the start and end points of the path,
which improves sampling efficiency, were done from the initial path to generate two distinct paths that would start in A and end in B. Based on the path lengths in those trials moves, the path length was set to 3.1 ps in the sampling simulations. During this equilibration phase, the proton transfer mechanism was observed to shift between proton transfer from a water molecule, mechanism 1 and proton transfer from the catalyst, mechanism 2. In the two paths chosen for sampling a water molecule was transferring the proton. The distance between the carbonyl carbon and the hydride and the distance between the carbonyl oxygen and the NH$_2$ group of the catalyst were considered as the most important distances in the reaction. Figure 4.3 shows the changes in those distances during the reaction for the initial path and the paths used to start the TPS sampling. The two paths are referred to as path 1.0

![Graph showing distances between hydride and carbonyl carbon and distances between carbonyl oxygen and NH$_2$ group for different paths](image)

**Figure 4.3:** Distance between the hydride and the carbonyl carbon and the distance between the carbonyl oxygen and the NH$_2$ moiety of the catalyst for the initial paths.
and path 2.0, while the simulations are referred to as simulation 1 and simulation 2. Based on the distance analysis, paths 1.0 and 2.0 differ significantly from the initial path and each other.

80 attempts to generate new trajectories were made, 40 from each starting path. 15 new trajectories were generated, 11 from path 1.0 and 4 from path 2.0, resulting in the acceptance rate of 28 % and 10%, respectively. The reaction consists of a sequential transfer of a hydride and a proton and this two step mechanism could be a reason for the low acceptance rate. The fractional probability of the paths in the transition path ensemble is shown in Figure 4.4. The decorrelation of the paths during the sampling is illustrated in Figure 4.5 that displays the important distance changes in time for the first five paths from simulation 1. It shows that decorrelation in the carbon hydride distance occurs slower than in the hydrogen bond with the catalyst. Significant changes in the NH$_2$O bond can be obtained already in the next accepted path, however it can take up to five new paths for the C-H distance to decorrelate.

Although the proton was transferred via mechanism 1 in both of the initial paths, the mechanism changed during the sampling for both simulations. Mechanism 1 was observed for paths 1.1, 1.10, 1.11 and 2.1-2.3, while mechanism 2 occurred in paths 1.2-1.9 and 2.4. The paths with mechanism 1 had more statistical weight in the transition path ensemble, their fractional weight was 0.575. However, in view of the infrequent change of the mechanism more simulation data is needed in order to determine which mechanism is more likely. The average duration of the methoxide intermediate, calculated taking the path weight into account, was 0.88 ps. There was a significant difference in duration for the two mechanisms, 1.15 ps for the mechanism 1 and 0.52 ps for mechanism 2. Snapshots for the two pathways with highest weight for each mechanism, paths 2.2 for mechanism 1 and 1.5 for

---

**Figure 4.4:** Fractional weight of the generated paths in the transition path ensemble.

![Fractional weight of the generated paths in the transition path ensemble.](image-url)
Figure 4.5: Illustration of path decorrelation for simulation 1 by plotting the important distance changes during the reaction, the distance between the hydride and the carbonyl carbon and the distance between the carbonyl oxygen and the NH$_2$ moiety of the catalyst.

mechanism 2 are shown in Figure 4.6 and Figure 4.7, respectively. The first snapshot was taken when the Ru-H distance was equal to the H-C distance, as that was the transition state according to our previous constrained molecular dynamics simulations. The second snapshot is of the methoxide intermediate and the third snapshot is of the proton transfer when the proton was exactly between the donor and the acceptor atoms. The two paths do not show a significant mechanistic difference until the proton transfer. In both cases, during the hydride transfer, the formaldehyde oxygen only has two hydrogen bonds. This differs from the constrained dynamics case, where the reactant often had three hydrogen bonds at this point. In the TPS simulations, the third bond is formed first after the hydride transfer,
Figure 4.6: Snapshots of the important stages of the reaction for path 2.2. In this path the proton is transferred by a water molecule, mechanism 1. Selected distances are shown in Å, the hydride is enlarged and has a darker color.

Figure 4.7: Snapshots of the important stages of the reaction for path 1.5. In this path the proton is transferred by the catalyst, mechanism 2. Selected distances are shown in Å, the hydride is enlarged and has a darker color when the methoxide intermediate is formed. Eventually, a proton is transferred along one of this hydrogen bonds, while the other two are remaining strong.

4-3.2 Analysis of the Reaction Coordinates

A detailed analysis of possible reaction coordinates was done in order to investigate the differences between the two mechanisms. Five reaction coordinates were analyzed: 1, the distance between the hydride and the carbonyl carbon, 2, the distance between the hydride and the ruthenium atom, 3, the distance between the NH₂ group and the carbonyl oxygen, (referred to as O-NH₂), 4, the distance of the nearest hydrogen from either a water molecule or the NH₂ group to the carbonyl oxygen, and finally 5, H-coordination of the carbonyl oxygen. Six paths were picked to illustrate the changes in these coordinates in time, three from each mechanism. In order to have maximally decorrelated paths with highest possible weight, paths 1.1, 1.2, 1.5, 1.10, 2.2 and 2.4 were chosen.
The results for the reaction coordinates 1-4 for the paths with mechanism 1, proton transfer from water, 1.1, 1.10 and 2.2, are shown in Figure 4.8, while the results for the paths with mechanism 2, proton transfer from the catalyst, 1.2 1.5 and 2.4, are shown in Figure 4.9. As shown in the top graphs of those figures, the reaction is initiated by a sudden decrease of C-H bond, while the Ru-H bond distance remains unchanged. When these two bonds are equal and around 1.7 Å in distance, there is a slight increase in the Ru-H bond, while the C-H bond decreases slightly further. After this event, there is a period during which both the Ru-H and C-H distances fluctuate at values that are slightly larger than normal bond values, suggesting that these bonds are not completely broken and formed, yet. This stage can last between 0.2 and 1 ps, and tends to be shorter in mechanism 2. Following this period, the hydride separates further from the Ru atom, while the C-H distance decreases to the bond distance of around 1.1 Å. All sampled trajectories in this study show this behavior. The proton transfer part of the reaction does not happen until the end of this period, which could explain why the reaction mechanism is sequential. Full breaking of the Ru-H bond may be needed before the proton can be transferred. Constrained dynamics
Figure 4.9: Changes of the investigated reaction coordinates 1-4 in time for the paths with proton transfer from the NH$_2$ moiety of the catalyst, mechanism 2.

studies also showed that the C-H distance decreases significantly before any changes in the Ru-H bond are observed. However, while it is an efficient method for obtaining free energy barriers, constrained dynamics does not necessarily capture all the dynamical features of a reaction mechanism.

As shown in the bottom graphs of Figure 4.8 and Figure 4.9, a hydrogen bond between the NH$_2$ group of the catalyst and formaldehyde oxygen is formed before the hydride transfer. The bond distance decreases when the hydride is transferred, suggesting that the NH$_2$ moiety is important for the reaction, even when it does not transfer the proton. This hydrogen bond breaks after the hydride transfer for mechanism 1 trajectories, this can happen before or after the proton transfer. The distance of the closest hydrogen to the carbonyl oxygen is decreased after the hydride transfer. For some paths, a proton transfer that is quickly reversed is seen, eventually a proton is transferred permanently. Note, until the proton transfer, the closest hydrogen is usually from a water molecule and not the NH$_2$ group. This holds for both mechanisms.

The solvation of the carbonyl oxygen was further investigated by also calculating the
Figure 4.10: Distances of the three closest hydrogens that are able to provide hydrogen bonds to the carbonyl oxygen. H1 is the closest hydrogen, H2 is the second closest and H3 is the third closest. Top graphs show the results for mechanism 1, while bottom graphs show the results for mechanism 2.

Distances of the second closest and third closest hydrogens, see Figure 4.10. Initially, this oxygen has one hydrogen bond, just as in the constrained dynamics simulations, and after the hydride transfer it gradually forms two more bonds. These bonds get shorter with time, until a proton is eventually transferred. Exchange of water molecules that are hydrogen bonded to the carbonyl oxygen is rarely observed before the proton transfer. In all paths, except path 1.10, the carbonyl oxygen has three strong hydrogen bonds, with length less than 1.8 Å, when a successful proton transfer occurs. In contrast, in most unsuccessful proton transfer attempts this oxygen has only two strong hydrogen bonds. Therefore, a three hydrogen bond configuration could be important for a successful proton transfer. In that case, the reaction mechanism could be sequential because of the rearrangement of the solvent around the carbonyl atom between the hydride and proton transfers. However, in the constrained dynamics simulations a configuration with three strong hydrogen bonds around the formaldehyde oxygen can be stable for a long time without a proton transfer, suggesting
that other factors may also be important for this step.

According to the analysis of the reaction coordinates and the solvation of formaldehyde, the two reaction mechanisms appear to be very similar. The only difference is that the duration of the methoxide intermediate and the breaking time of the Ru-H bond is longer in mechanism 1. Therefore, the path pairs for which the mechanism switched were investigated in order to understand the differences between the two mechanisms. The switches in the mechanism occurred for paths 1.1 and 1.2, 1.9 and 1.10, and 2.3 and 2.4. The reaction coordinates 1-4 for the pairs of paths are plotted in Figure 4.11. For all of the path pairs, there are almost no differences during the hydride transfer for these coordinates. Evidently, two pathways with an almost identical hydride transfer step can have different mechanisms for the proton transfer, which suggests that these two steps are not significantly correlated. After the hydride transfer, a decorrelation in the O-NH₂ distance is observed in two of the

![Figure 4.11: Comparison of the reaction coordinates for the path pairs for which the proton transfer mechanism is switched. Top graphs, black and blue lines show the R-H distance while red and green lines show the C-H distance for the path pairs. Bottom graphs, black and blue lines show the O-NH₂ distance while red and green lines show the distance of the nearest proton.](image-url)
the three cases, this distance becomes larger for mechanism 1 than for mechanism 2. For the paths 1.9 and 1.10 no difference in this distance is seen until the proton transfer. The nearest hydrogen distance does not differ for the three path pairs until the proton transfer, suggesting that the solvation of the methoxide intermediate can be very similar for both mechanisms. Based on these observations, both the NH₂ group and water molecules could be potential proton donors and random fluctuations may decide which of them actually transfers the proton. This is supported by our study of catalyst deprotonation in Chapter 3, where the deprotonation barrier for the catalyst was close to the barrier for autoionization of water in solution. One difference between the mechanisms is that proton transfer through mechanism 2 needs to happen before the hydrogen bond between the catalyst and methoxide is broken, while mechanism 1 does not have a time limitation. This could explain the longer duration of the methoxide intermediate for mechanism 1.

4-4 Summary and Conclusions

The transfer hydrogenation of formaldehyde with RuTsDPEN model catalyst was studied in explicit solution with reactive path sampling. It was confirmed that the mechanism is sequential with the hydride transfer preceding the proton transfer. New dynamical features of the hydride transfer step, not directly observed in constrained molecular dynamics simulations, were found. The hydride transfer started with a quick shortening of the C-H distance, followed by a longer period of up to 1 ps during which the Ru-H and C-H bonds fluctuated at a distance that is slightly larger than normal bond distance. The proton transfer did not occur until the Ru-H bond was fully broken and the C-H bond fully formed. The hydrogen bond between the NH₂ group of the catalyst and the formaldehyde oxygen decreased during the hydride transfer for all of the trajectories, suggesting that it plays an important role in the mechanism, even if it does not transfer the proton. However, the strongest hydrogen bond of the formaldehyde oxygen is usually with a water molecule and not the catalyst. Investigation of the solvation shell around the oxygen of the methoxide intermediate showed that prior to a successful proton transfer, it usually has three very strong hydrogen bonds. Formation of those bonds can take up to 1 ps after the start of the hydride transfer. The mechanism could be sequential because it takes time to fully break the Ru-H bond and to form three strong bonds around the methoxide intermediate. Successful proton transfers almost always happened after these structural changes.

Two slightly different mechanisms were found: the proton could be transferred by either a water molecule or the NH₂ moiety of the catalyst. While proton transfer from water is more likely according to these simulations; further simulations are needed to confirm this. Analysis of the reaction coordinates showed similar behavior for both mechanisms. The only observed difference is that the breaking of the Ru-H bond and the duration of the methoxide intermediate are longer on average for paths in which the proton is transferred by water. Comparison of path pairs for which the mechanism switched, showed almost no differences during the hydride transfer, suggesting that this step is decorrelated from the proton transfer. Some path pairs show strong correlation all the way until the proton trans-
Reactive Path Sampling of Transfer Hydrogenation.

This suggests that both the NH$_2$ group of the catalyst and water molecules are likely proton donors, and which of them eventually transfers the proton is decided by chance. It is possible that other reaction coordinates, not investigated here, play an important role. Comittor analysis of the reaction coordinates is required to see if other variables are needed in describing this reaction. Another topic for future studies is quantum effects that could affect the proton transfer part of the mechanism. This study illustrates how including real kinetics in a mechanistic study, for example via transition path sampling, can provide a unique insight into a catalytic reaction and explain the observed mechanism.

4-5 References


