Ruthenium-Catalyzed Secondary Amine Formation Studied by Density Functional Theory

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Amines are a ubiquitous class of compounds found in a variety of functional organic building blocks. Within the past years, hydrogen autotransfer catalysis has evolved as a new concept for the synthesis of amines. A thorough understanding of the mechanism of these reactions is necessary to design optimal catalysts. We investigate secondary amine formation catalyzed by a NNNN(P)Ru-complex and provide understanding on the three reaction steps involved. We find that the ligand has to open one coordination site in order to allow the formation of a metal hydride intermediate. In a second step, a condensation reaction, which could also happen uncatalyzed in solution, is significantly enhanced by the presence of the ruthenium complex. The back-transfer of the hydride to the substrate in a third step regenerates the catalyst.

1. Introduction

Amines are a ubiquitous class of compounds found in a variety of functional organic building blocks. Hydrogen borrowing reactions\[^{[1-15]}\] are one class of the various available synthesis routes, which reuses all hydrogen atoms, in contrast to dehydrogenative coupling with \(\text{H}_2\) production.\[^{[16-18]}\] Within the past years, hydrogen autotransfer catalysis has evolved as a new concept for the synthesis of amines.\[^{[19-24]}\] This strategy addresses some of the most important short-comings of traditional synthetic routes connected to the use of reactive alkylating agents, i.e., the need to prepare these reactive reagents through, e.g., halogenation reactions, their problematic bio-activities and the amount of by-products (e.g., salts, overalkylation products) produced in the C–N bond formation. The concept is shown in Figure 1.

Accordingly, alcohols are employed as alkylating reagent and the entire concept relies on the use of the well-elaborated reaction portfolio of the carbonyl group.\[^{[26,27]}\] Upon catalytic dehydrogenation of the alcohol a carbonyl group and a metal hydride are generated in small amounts. The former undergoes a fast condensation reaction, e.g., with an amine to form an imine and water as by-product. This imine is hydrogenated by the metal hydride species to deliver the desired amine with regeneration of the active catalyst. Despite the progress that has been made in the field of hydrogen autotransfer catalysis, hardly any mechanistic investigations have been reported.\[^{[28,29]}\] However, a deeper understanding of factors that influence the catalytic reaction is required to develop more efficient catalytic systems. In the present report we summarize the findings of an in-depth theoretical investigation that addresses some of the most important issues connected to hydrogen autotransfer catalysis: (i) how fast is the dehydrogenation of the alcohols/hydrogenation of the aldehyde as compared to the hydrogenation of the imine?; (ii) what is the mechanism of the hydrogen transfer between alcohol to catalyst and catalyst to

![Figure 1. Schematic concept of the hydrogen autotransfer catalysis. Reproduced with permission from Ref. [25]. Copyright 2013 Wiley-VCH.](image-url)
imine?; and (iii) does the catalyst influence the rate of the condensation reaction?

One of the authors reported\textsuperscript{[25]} the synthesis and catalytic evaluation of a novel type of NNNN(P)Ru-complex (Figure 2) that showed high activity in the catalytic hydrogen autotransfer condensation of primary amines and alcohols. Systematic evaluation of substitution and counter-anion effects led to the identification of the most active catalyst and indicated the right balance between electron-richness and -poorness of the metal center to be crucial for good turnover rates. Moreover, the catalyst design was based on the hypothesis that the highly lipophilic ligand environment at the penta-coordinated metal center would lead to an increased release of water within the condensation step. This, however, would include that the condensation step would take place within the coordination sphere of the catalytic center.

The results of these experimental investigations and the structure shown in Figure 2 were used as a starting point for our calculations.

In the pre-catalyst, see Figure 2, the metal center is octahedrally coordinated by a tetra-dentate ligand at two of the equatorial and at the axial positions, the remaining equatorial ones are occupied by PPh\textsubscript{3} and chloride. The counter-ion is hexafluorophosphate PF\textsubscript{6}-. The results of these measurements are used as the initial structure for our calculations.

As an exemplary reaction, we study the reaction of benzyl alcohol with aniline to form benzyl-phenylamine. Typical experimental conditions are toluene as a solvent and 100 °C.\textsuperscript{[25]} The proposed catalytic cycle contains the following steps, see Figure 3. It is initiated by the deprotonation of benzyl alcohol.

The resulting alcoholate replaces chloride to form structure 1. Starting from this, the alcoholate is transformed to benzaldehyde 5 by β-H-elimination. The resulting benzaldehyde reacts with aniline. This step could happen uncatalyzed in solution or activated by the catalyst. The reaction results in the corresponding hemiaminal 8, again being linked to the complex. Subsequently, the hemiaminal is transformed to the imine forming water as by-product 12. After displacement of the water molecule, the hydride migrates back to the substrate, which leads to the deprotonated benzyl phenylamine 18. Protonation results in the final product.

2. Results and Discussion

2.1. Part 1: β-H-Elimination from Alcoholate to form the Aldehyde

The reaction is initialized by a deprotonation of the alcohol to form the alcoholate. This step is facilitated by the alkaline reaction condition. Since it likely happens non-catalyzed in solution, we refrain from modeling it here. The resulting benzyl alcohol replaces the chloride of the pre-catalyst to form the active catalyst 1, which is the starting point of our investigation.

In 1, benzyl alcoholate is coordinated to ruthenium cis with respect to PPh\textsubscript{3}. Structure 1 forms benzaldehyde via a β-H-elimination as shown in Figure 4. In the lowest-energy path we found, the hydride migrates from the substrate to Ru(II) and displaces one of the ligands in an axial position, also cis to PPh\textsubscript{3}. This involves the breaking of the coordinative bond between Ru(II) and pyridine, which requires to overcome a substantial

\textbf{Figure 2.} Molecular structure of the pre-catalyst and its X-ray structure. Reproduced with permission from Ref. [25]. Copyright 2013 Wiley-VCH.

\textbf{Figure 3.} Overview of the reaction mechanism. The β-H-elimination from 1 to 5 is followed by the condensation reaction via 8 to 12. The product release to reach 21 is facilitated by the next reactant molecule.

\textbf{Figure 4.} Scheme of part 1, the oxidation of benzyl alcoholate 1 to benzaldehyde in the π-complex 3 and σ-complex 5. ΔG in kJ mol \textsuperscript{-1} at the M06/def2-TZVP//GFN2-xTB level is given in parentheses relative to 1.
energy barrier of 130 kJ mol\(^{-1}\) (\(2_{TS}\)), see Figure 4. The geometry of the transition state \(2_{TS}\) is depicted in Figure 5.

Alternative hydride positions were investigated. The hydride \(\text{trans}\) to \(\text{PPh}_3\) is less stable, probably due to the electron-pushing \(\text{trans}\)-effect. By contrast, the hydride \(\text{trans}\) to the substrate is energetically slightly favored because of the electron withdrawing \(\text{trans}\)-effect by the oxygen atom, but steric hindrance impedes any conceivable pathway to such a structure.

The resulting aldehyde coordinates the ruthenium center either in a \(\pi\) coordination of the \(\text{C}=\text{O}\) bond, 3, or in a \(\sigma\) coordination via a lone pair of the oxygen atom, 5. Both structures are similar in energy with 110 kJ mol\(^{-1}\) and 108 kJ mol\(^{-1}\), respectively, with a small activation barrier of 29 kJ mol\(^{-1}\) between them. Since the opening of the Ru–pyridine coordinative bond, which opens a second coordination site at Ru(II), requires considerable energy, we investigated alternative paths. The \(\beta\)-H-elimination could also happen on a single site, without opening of a pyridine ligand. In such a case, the equivalent to structure 5 has the hydride bound to Ru, but the aldehyde unbound. Such a structure is preferable in energy, with \(-2\) kJ mol\(^{-1}\) it has almost the same free energy as 1, but the activation barrier to reach it is very high. The lowest path we found has a free-energy barrier of 223 kJ mol\(^{-1}\), insurmountable even at 100 °C. Furthermore, the following reaction steps are facilitated if the aldehyde is coordinated to Ru.

2.2. Part 2: Condensation Reaction

Aniline associates to the \(\sigma\) complex 5 forming structure 6, in which the amine is ideally placed to attack the activated aldehyde, leading to the hemiaminal 8, see Figure 6 for a schematic overview. The barrier for this reaction is with 145 kJ mol\(^{-1}\) of quite considerable height, see Figure 6. Energies are given relative to structure 6 to restrict the comparison to unimolecular reactions. In both, 6 and 8, the arrangement is stabilized by \(\pi\)-\(\pi\) interactions between the ligand and with the substrates. Aniline could attack 6 from the side of the hydride or the pyridine ligand. The former is favored for steric reasons. The hemiaminal 8 is chiral. However, its steric information is lost during the subsequent steps.

A proton shift leads to dehydratization of the hemiaminal 8 via 9\(_{TS}\), depicted in Figure 5, to form the imine 10. This is facilitated by the catalyst, to which the water-oxygen remains
coordinated. In 10, the substrate is coordinated to the catalyst only via a hydrogen bond. This step is exothermic with a moderate activation energy of 72 kJ mol\(^{-1}\).

The condensation reaction could, in principle, also proceed without catalyst. This would include the dissociation of the aldehyde from the catalyst, followed by an attack of the amine to the aldehyde and a dehydratization. However, the barriers for such a transformation without catalyst are much higher, see Figure 7. The activation energy for \(\tau_6\), the attack of the amine to the aldehyde, is raised by 21 kJ mol\(^{-1}\), while the activation energy for the dehydratization is raised by 121 kJ mol\(^{-1}\) to 234 kJ mol\(^{-1}\) above the energy of 6 by removing the catalyst. The activation is caused by the metal center, which withdraws electron density from the oxygen and increases the polarity of the C=O bond. Thus, the nucleophilic attack by aniline and the hydrogen transfers are facilitated.

Before the hydride can be transferred back to the imine, some rearrangement steps are required. One possible path is the one outlined here from 10 to 16. However, this is not the only conceivable path and it may well be that it is not the lowest-energy path. Firstly, the substrate is converted from \(\text{trans}\) to \(\text{cis}\) (10 to 12). This reaction is, as expected, slightly endothermic by 20 kJ mol\(^{-1}\). It has a significant barrier of 135 kJ mol\(^{-1}\). In the \(\text{cis}\)-conformation the imine substrate can be rotated easily (12 to 14), to align the aliphatic carbon towards the hydride. Later, such an arrangement is necessary in order to move the hydride back to the substrate. Before the hydride transfer, the water molecule is eliminated (15\(_{1s}\) see Figure 5) with an activation energy of 107 kJ mol\(^{-1}\). After that, in structure 16 the \(\text{cis}\)-imine is coordinated to the catalyst via its nitrogen atom. The barriers 11\(_{1s}\)-15\(_{1s}\) were found by NEB calculations on the GFN2-xTB level with single point calculations at the DFT level rather than full transition state searches. Thus, the values for these barriers are less reliable than the fully optimized ones. However, these rearrangements from 10 to 16 constitute conformational changes, but no chemical reactions. They have little influence on the overall cycle.

We investigated several alternative routes. For example, rather than \(\text{H}_2\text{O}\) formation at 9, we investigated paths of hydride transfer from Ru to the hemiaminal with \(\text{OH}\) remaining coordinated to Ru. The barriers for such paths were rather high, however.

Finally, the product amine 18 is obtained by hydride transfer from the catalyst back to the imine. The aliphatic carbon in 16 is already positioned close to the hydride. The migration takes place easily via a quadratically planar transition state, 17\(_{1s}\) with an activation energy of only 23 kJ mol\(^{-1}\). The reaction is significantly exothermic, which is dominated by the re-coordination of the pyridine ligand to Ru. The resulting secondary amine is still deprotonated and is coordinated to the Ru-center of the catalyst. A further step is necessary to release the product.

### 2.3. Part 3: Product Release and Replacement by the Next Substrate Molecule

In order to release the product, the amine has to be protonated, see Figure 8. This proton can be donated by the next substrate molecule, benzyl alcohol 19. Benzyl alcohol can be coordinated to the ruthenium center by removing a pyridine ligand, but that would cause a rather high barrier of 211 kJ mol\(^{-1}\). However, a much lower barrier is obtained if the proton transfer happens in a concerted reaction with the exchange of ligands via 20\(_{1s}\). In this concerted transition, O of benzyl alcohol approaches Ru, N of the product dissociates from Ru and the proton is transferred from O to N, see Figure 5. This rearrangement has a barrier of 128 kJ mol\(^{-1}\) and results in the final product, the neutral amine, and the next deprotonated substrate to continue the cycle.

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**Figure 7.** Energy profile for the catalyzed (black) and non-catalyzed (red) condensation reaction. Free energies are given relative to the respective states 6, at the M06/def2-TZVP//GFN2-xTB level including thermal corrections at the GFN2-xTB level.

**Figure 8.** Scheme of part 3, the release of the product and the initiation of the next catalytic cycle. \(\Delta G\) in kJ mol\(^{-1}\) at the M06/def2-xTZVP//GFN2-xTB level is given in parentheses relative to 19. Dashed lines in 20\(_{1s}\) correspond to bonds that are broken and formed in the transition, see text.
We also tested if a water molecule is involved in this process, but we neither found a path in which water protonates the amine directly nor one where substitutes the pyridine ligand. Thus, after water is removed, it does not seem to play any role in the catalytic cycle.

Our findings are consistent with the experimental observations. However, this does not mean that they are necessarily the only possible paths. While our level of theory can be assumed to be fairly reliable, other functionals or higher levels of theory may result in different barriers and different minimal paths. The sampling of possible paths is, in our opinion the most important issue for this reaction. We have investigated several side paths and presented the main lowest-energy path. However, especially in the rearrangement steps from 10 to 16 different orders of the steps and, thus, different paths are easily possible.

There is no clear rate-limiting step in the reaction. We found several barriers of approximately equal height. This is a typical situation for an optimized catalytic cycle in which the conditions are optimized for several steps concurrently. The largest barriers we observed are the β-H-elimination and the condensation reaction from 6 to 8. The reverse reaction of the β-H-elimination, from 16 to 18 has a comparably low barrier because it is facilitated by reformation of the Ru–pyridine bond.

We found that the backbone of the ligand of the catalyst complex, including it two benzyl groups, hardly affect the catalytic cycle. In future studies, we attempt to immobilize this catalyst on a porous support. These benzyl groups will be suitable anchoring positions for catalyst immobilization. By contrast, the pyridine ligands have to remain flexible in order to allow an opening of a second accessible site at the Ru center.

3. Conclusion

We have studied the hydrogen autotransfer catalytic reaction of secondary amine formation, catalyzed by a NNNN(P)Ru-complex. The first step is a β-H-elimination, which leads to the opening of one Ru–pyridine bond. The following condensation reaction with aniline is more likely to happen activated by the Ru complex than free in solution. Hydride back transfer is facilitated by the re-formation of the Ru-pyridine bond. The protonation of the resulting secondary amine is coupled by the next alcohol molecule in the catalytic cycle is coupled to product release. Our mechanism explains the hydrogen autotransfer reaction and provides hints for possible anchoring sites for catalyst immobilization in molecular heterogeneous catalysis approaches.

Computational Methods

All geometries were optimized with the semiempirical method GFN2-xTB. Single point energies were calculated at the resulting geometries at the M06/def2-TZVP level. For several intermediates, geometries were also optimized at the M06/def2-SVP level. The results are close to those of the optimization at the GFN2-xTB level as reported in the Supporting Information. Gas-phase calculations were used throughout. A comparison to GBSA solvation with toluol showed only small differences as shown in a comparison in the supporting information.

All geometry optimizations were carried out with the DL-FIND software package as implemented in ChemShell. Nudged elastic band (NEB) calculations were performed to obtain initial geometries in the vicinity of the transition state, followed by transition state (TS) optimizations with the dimer method as implemented in DL-FIND.

Hessian calculations were performed on the same level of theory as the geometry optimizations, i.e., GFN2-xTB, to confirm the nature of the stationary points. In addition, intrinsic reaction coordinate (IRC) calculations are carried out to verify which minima the TSs connect.

Zero point energies (ZPE) and thermal corrections at 100°C were computed using the rigid rotor, harmonic oscillator (RRHO) approximation. For the thermal corrections, frequencies smaller than 100 cm⁻¹ are raised to 100 cm⁻¹ to improve the validity of the RRHO model.

Supporting Information

Cartesian coordinates of all structures reported here are provided as Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

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