Ruthenium Catalyzed Reductive Transformation of Itaconic Acid and Ammonia Into 3- and 4-Methyl-pyrrolidone
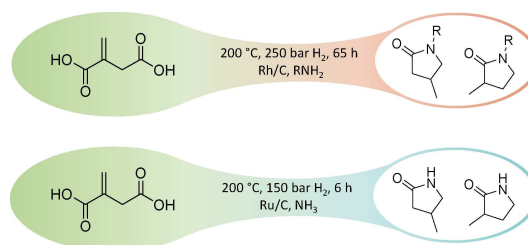
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The reductive transformation of biogenic carboxylic acids and ammonia presents a promising route to access pyrrolidones as N-containing bio-based fine chemicals. Herein, we report the first approach to convert itaconic acid to N-unsubstituted pyrrolidones. The reaction was carried out in low amounts of water as solvent with hydrogen as reduction agent and ammonia as nitrogen source. A Ru/C catalyst was found to be highly active for this reaction. Furthermore, a coherent reaction network could be proposed. Catalyst recycling and variation of substrates demonstrate both the robustness and broad scope of the presented catalytic system.

Lignocellulose is a sustainable carbon resource offering access to promising platform chemicals such as biogenic carboxylic acids. Itaconic, succinic and levulinic acid were named by the US Department of Energy as 3 out of 12 possible biobased platform chemicals produced either by fermentation or via chemo-catalysis.[1] Various investigations focused on their reduction to C$_4$ and C$_5$ building blocks covering γ-butyrolactone, butanediol or tetrahydrofurans.[2,3] In contrast, their transformation into N-containing motifs as important building blocks of chemical industry has been hardly addressed.

The reductive amination of biogenic carboxylic acids with amines or even ammonia allows direct access to N-containing molecules such as pyrrolidones. Pyrrolidones present an important class of petrochemical N-heterocycles with prominent examples such as 2-pyrrolidone or N-methylpyrrolidone (NMP) for solvent applications and vinylpyrrolidone (NVP) as a monomer of polyvinylpyrrolidone (PVP). Currently, pyrrolidones are predominantly produced from fossil acetylene and formaldehyde via γ-butyrolactone.[4] Renewable approaches however are scarce with only few studies tackling the reductive

amination of biogenic carboxylic acids for the synthesis of N-alkylated pyrrolidones using primary amines as nitrogen source.[3,5–8,9] Homogeneously catalysed systems using stoichiometric reduction agents such as formic acid in order to operate at mild reaction conditions were reported. Active precious metal complexes e. g. based on ruthenium[10] or iridium[6] served as catalysts. Despite noticeable activity, long reaction times of more than 10 h were necessary. For supported metals, hydrogen served as reducing agent under rather harsh reaction conditions. Manzer et al. reported the conversion of levulinic acid with primary amines on solid catalysts in a patent in 2004.[5] The highest activity was found for Pt, Pd and Ir as the catalytically active metals. The reactions proceeded at 150 °C and 30–60 bar H$_2$ enabling excellent yields of 1-alkyl-5-methyl-2-pyrrolidones of more than 90%. Several reaction pathways for the conversion of levulinic acid to pyrrolidones were proposed. First the carbonyl function is converted into the imine which is consecutively reduced and cyclized to 5-methylpyrrolidone.[7,8,12] White et al. described the synthesis of N-methylpyrrolidone (NMP) starting from succinic acid using ammonia, methanol and a heterogeneous Rh catalyst. They proposed a reaction network composed of dehydration, amination, cyclization and a subsequent reduction steps. They also suggested that a 2-step synthesis, in which first the N-methyl-succinimide is isolated and then consecutively reduced, would be beneficial.[3] The transformation of itaconic acid to pyrrolidones is described in a single patent by BASF.[11] The product scope, however, is limited to N-alkylated pyrrolidone mixtures of 3- and 4-methyl-N-alkyl-2-pyrrolidones. Best results were reached for the conversion of itaconic acid with methylamine resulting in 1,3- and 1,4-dimethylpyrrolidone in a ratio of 2:1. A supported Rh catalyst enabled the highest yield of 91% at 200 °C and 250 bar, however, the reaction time was 65 h (Scheme 1).

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Scheme 1. Previous work[11] on the conversion of itaconic acid to N-alkylated pyrrolidones (R = C$_1$–C$_{24}$) compared to this work.
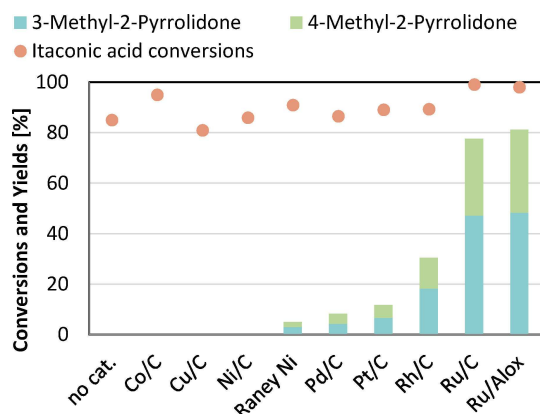
Figure 1. Conversion of itaconic acid to 3- and 4-methyl-2-pyrrolidone with several commercial catalysts. Reaction conditions: 200 °C, 150 bar H_2, 5 bar NH_3, 1.5 g itaconic acid, 1.5 g H_2O, 75 mg catalyst, 4 h.

N-unsubstituted pyrrolidones are hardly targeted. 2-Pyrrolidone can for example be accessed via succinic anhydride.[13] Patent literature of the 1960s reported synthesis of N-unsubstituted pyrrolidones from succinic acid over Ni, Co and their oxides as catalysts at 230 °C, 250 bar and 24 h yielding up to 80 % 2-pyrrolidone.[14,15] Manzer et al. described the transformation of levulinic acid with ammonia, only reaching low yields of about 2 %.[5] Du *et al.* reported a supported gold catalyst that converted levulinic acid into 5-methylpyrrolidone in yields of up to 85 % after 16 h reaction time.[16]

We herein demonstrate for the first time the efficient conversion of itaconic acid to N-unsubstituted pyrrolidones over supported metal catalysts, propose a reaction network based on reaction intermediates and emphasize broader applicability for other biogenic carboxylic acids as substrates.

Despite general feasibility, major challenges to overcome comprehend relatively harsh conditions and long reaction times. We included commercial metal catalysts active in hydrogenation as well as candidates based on the discussed literature[3,5,11,15] in a first set of experiments (Figure 1). High conversion of itaconic acid after only 4 h in all cases can be assigned to a thermally driven amide formation discussed later

within this report. Surprisingly, Co, Ni and Cu, named in patents for succinic acid as substrate, did not facilitate pyrrolidone formation from itaconic acid.[14,15] Also supported Pd, Pt and Rh, frequently reported as active to form N-alkylated pyrrolidones,[3,7,11] led to low yields. In contrast, supported ruthenium catalysts both with activated carbon and alumina as support provided high pyrrolidone yield in short reaction time. In contrast to the other precious metals, ruthenium cannot only activate H_2 but also C—O-bonds.[17] Therefore, we suggest this property to be of importance for the high activity. Since carbon supports usually possess a superior long-term stability than Al_2O_3 in aqueous media[18], Ru/C was chosen for further optimization of the reaction conditions.

Reaction temperature, hydrogen pressure and water addition influence the transformation of itaconic acid to 3- and 4-methyl-2-pyrrolidone (Figure 2). The yield of pyrrolidones rises with temperature and hydrogen pressure. At 150 °C no pyrrolidones and only low amounts of intermediates are formed (Figure S3), while 65 % yield can be reached at 200 °C and 2 h reaction time. According to a low conversion below 180 °C, we suggest a high activation energy of the thermally driven steps. Even at 200 °C the formation of the imide seems to be rate determining as imide concentration remains low in the course of the reaction (Figure 3). For rising hydrogen pressure, we observed an almost proportional increase of the 2-pyrrolidone yield with 20 % at 50 bar and more than 60 % at 150 bar, respectively. Two aspects have to be considered: Higher pressures increase the concentration of dissolved H_2 in the condensed phase and thereby the reaction rate of the reduction step increases. As the reaction mixture is very concentrated and Ru activates carbonyl functions, high H_2 pressures could be required to allow sufficient hydrogen coverage of the catalyst. At low hydrogen pressure faster stirring increased the yield, while no major influence occurred at high pressures. Therefore, gas-liquid mass transfer appears to become decisive at low pressures. Furthermore, the equilibrium of gaseous and liquid substrates can be shifted towards condensed compounds by increasing the pressure potentially increasing availability of ammonia and shifting the equilibrium towards the imide. The ammonia partial pressure, however, has no profound influence on the catalyst activity (see Figure S6). Interestingly, the amount of water added to the reaction mixture poses a crucial influence. Without any solvent,
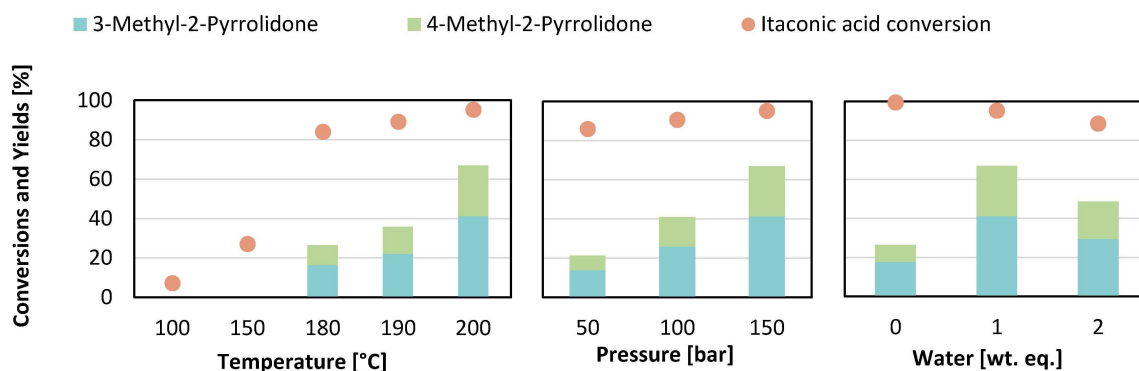

Figure 2. Conversion of itaconic acid to 3- and 4-Methyl-2-Pyrrolidone with varying reaction conditions. Standard reaction conditions were 200 °C, 150 bar H_2, 5 bar NH_3, 1.5 g itaconic acid, 1.5 g water, 37.5 mg 5 wt.% Ru/C, 2 h.

pyrrolidone yield reaches 30%. We assign this finding to undesired side reactions of the methylene group as under the same reaction conditions the saturated methylsuccinic acid can be converted to pyrrolidones in yields of up to 90%. For one equivalent of water, yield enhances to 65%. In this case, the itaconic acid is diluted and the methylene group is reduced rapidly. No itaconic acid can be identified in the reaction mixture when the reaction temperature reaches 200°C. For even higher water addition, both conversion and yield decrease. **F** illustrates the reaction network including several dehydration steps. Accordingly, higher water contents shift the equilibrium towards the substrate. This hypothesis is substantiated by the fact that the concentrations of methylsuccinic acid and the monoamides are higher in comparison to experiments with lower amounts of water (Figure S4). Overall, high pressures and temperatures and the addition of small amounts of water are beneficial for an efficient conversion of itaconic acid to 3- and 4-methyl-2-pyrrolidone.
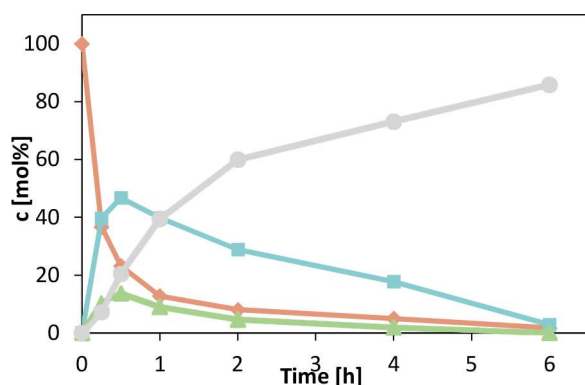

Figure 3. Concentration-time profile for the catalytic transformation of itaconic acid to 3- and 4-methylpyrrolidone at 200°C, 150 bar H_2, 5 bar NH_3, 3 g itaconic acid, 3 g water, 75 mg 5 wt.% Ru/C. Assignment: ♦: Itaconic acid, ●: Pyrrolidones, ■: Amides, ▲: Imide. The corresponding structures can be found in Scheme 2.

Figure 3 illustrates the reaction progress with more than 85% yield after 6 h under optimised conditions. At longer reaction times the yield increases up to 90%. The missing 10% can probably be assigned to oligomeric species as the amount

of over-reduced products remains negligible ($<1\%$). An isomeric mixture of 3- and 4-methyl-2-pyrrolidone forms and several reaction intermediates can be identified. Scheme 2 summarises the proposed reaction pathway. The first reaction step is the rapid reduction of the terminal methylene group and takes place during the initial heating of the autoclave. Itaconic acid is already completely converted at the time the autoclave reaches reaction temperature. Due to ammonia and water being present in the reaction mixture, the carboxylic acid groups of methylsuccinic acid are in equilibrium with the amides. Two isomeric monoamides and the diamide of methylsuccinic acid form. The amides can cyclize by dehydration or deamination to form 3-methylsuccinimide.

At the applied reaction conditions all amination and dehydration reactions are fast equilibrium reactions, which explains why amides and imide reach the maximum concentration simultaneously after 30 minutes (see Figure 3). The transformation of methylsuccinic acid to 3-methylsuccinimide is thermally driven and not influenced by Ru/C (see Figure S1 and S2). White *et al.*[3] proposed a comparable path for the direct conversion of succinic acid to 2-pyrrolidones. The final reaction step is the catalytic reduction of 3-methylsuccinimide to form the two pyrrolidone isomers. The formation of 3-methyl-2-pyrrolidone is favoured, as the 2 isomers form in 2:1 ratio. This is probably caused by steric hindrance of the methyl group adjacent to the keto group.

After parameter optimization and insight in the reaction network, recycling experiments were performed (Figure 4). Ru/C could be recycled five times without loss of activity. The pyrrolidone yield remained constant throughout these experiments confirming high catalyst stability.

As the reaction was only performed in small scale (1.5 g itaconic acid), we scaled the reaction up using a 500 ml stirred batch reactor with 50 g itaconic acid substrate. A longer heating process increased the reaction time to 10 h. Side product formation became more pronounced. Nevertheless, we achieved 80% pyrrolidone yield under the same reaction conditions as for the small scale confirming a general scalability of the underlying reaction. Via distillation under reduced pressure (0.03 mbar), we could isolate a mixture of 3- and 4MP (bp.: 64–67°C) with a purity of $>99\%$.
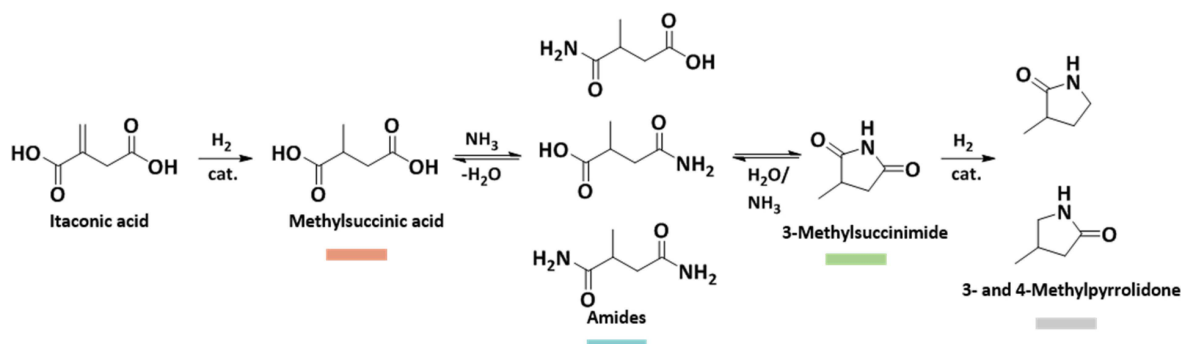
Scheme 2. Reaction system of the conversion of itaconic acid to 3- and 4-methyl-2-pyrrolidone.

Besides itaconic and methylsuccinic acid, also other biogenic carboxylic acids were tested to demonstrate broader applicability of the catalytic system. Indeed, also malic, maleic, levulinic and succinic acid could be transformed into the corresponding pyrrolidones, however, with lower yields for the reaction conditions optimised for itaconic acid (Table 1). In case of levulinic

Table 1. Conversion of different biogenic carboxylic acids to pyrrolidones.[a]

Substrate	X [%]	Y [%]	Productivity[b]
Itaconic acid	98	83	391
Methylsuccinic acid	99	80	371
Levulinic acid	100	45	237
Succinic acid	99	47	244
Maleic acid	80	37	195
Malic acid	85	27	123

[a] Reaction conditions: 200 °C, 150 bar H_2, 5 bar NH_3, 1.5 g Substrate, 1.5 g water, 75 mg 5 wt.% Ru/C, 4 h. [b] [mol(Pyrrolidone)/mol(Ru)/h]

acid, we assign the moderate yield to a different reaction pathway compared to dicarboxylic acids.[7] The lower productivity for the other dicarboxylic acid could be related to undesired side reactions or higher stability of the intermediate imide. Methylsuccinic acid as substrate enables pyrrolidone formation with high selectivity even without the addition of water reaching above 90% yield within 4 h reaction time. Therein, water addition decreases the yield to 80% (Figure S5). The results clearly demonstrate that reaction conditions need to be optimised for every substrate individually, though, the catalytic system is generally applicable for a one-step pyrrolidone formation.

In summary, we could demonstrate the direct catalytic transformation of itaconic acid to 3- and 4-methylpyrrolidone using molecular hydrogen and ammonia as reactants. Supported ruthenium provided high activity and selectivity together with excellent stability upon recycling. A coherent reaction network based on the identified intermediates and concentration-time profiles with dehydration, amination, cyclization and hydrogenation steps could be proposed. A broader substrate scope also emphasised general applicability of the catalytic system expanding the portfolio of biogenic pyrrolidones.

Acknowledgements

Conflict of Interest
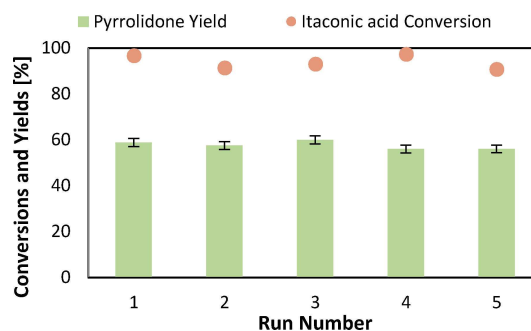
The authors declare no conflict of interest.

Figure 4. Recycling experiments with the Ru/C catalyst. Reaction Conditions: 200 °C, 150 bar H_2, 5 bar NH_3, 1.5 g itaconic acid, 1.5 g water, 37.5 mg 5 wt.% Ru/C, 2 h.

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