Hydrogenation of amides to methanol and amines with an iron-based catalyst. A computational study.

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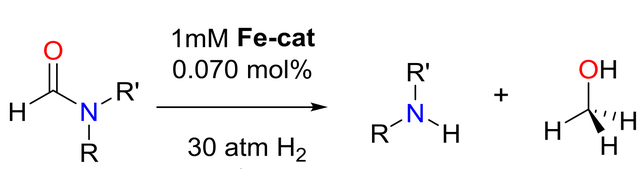
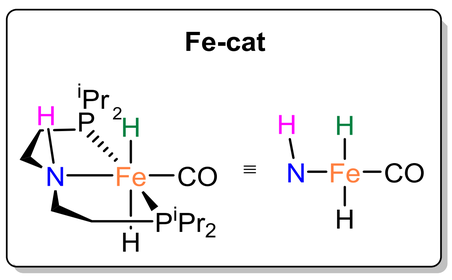
Introduction

Amides functionalities are among the most widely found groups in biologically active molecules, and their selective catalytic reduction is an important target for new synthetic methods. Recently the deaminative hydrogenation of several amides have been achieved in mild conditions with the Fe-catalyst shown in Figure 1.[1] In this work, we investigate computationally this reaction using formanilide and dimethyl formamide (DMF) as active and inactive substrates, respectively, and the co-catalytic effect of formanilide.



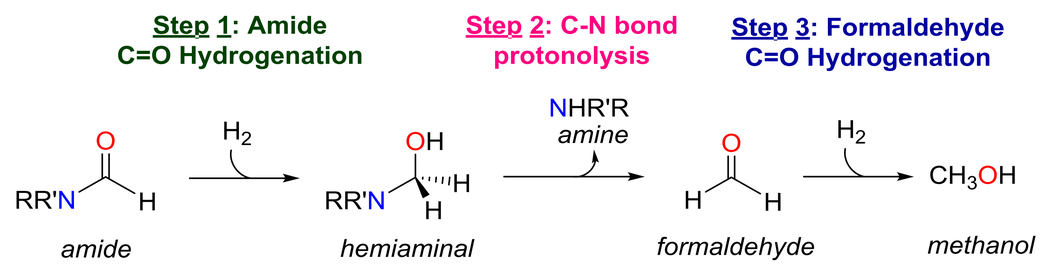


R = H; R' = Ph Conv. = 99.9%
R = R' = Me Conv. = 0 % (13.6%)*

Figure 1. Reaction under study (Left), and the catalyst used (right). * Using formanilide as co-catalyst, T = 120 ºC and P = 60 atm.

Elementary steps

The mechanism commonly proposed in the literature for the deaminative hydrogenation of amides involves the intermediates in figure 2.[2] The reaction consists in three steps, two endergonic and the last one exergonic. The hydrogenation of formanilide is completely displaced to products ($\Delta_r G$ = -10.1 kcal/mol), while the one of DMF is more reversible ($\Delta_r G$ = -1.5 kcal/mol).



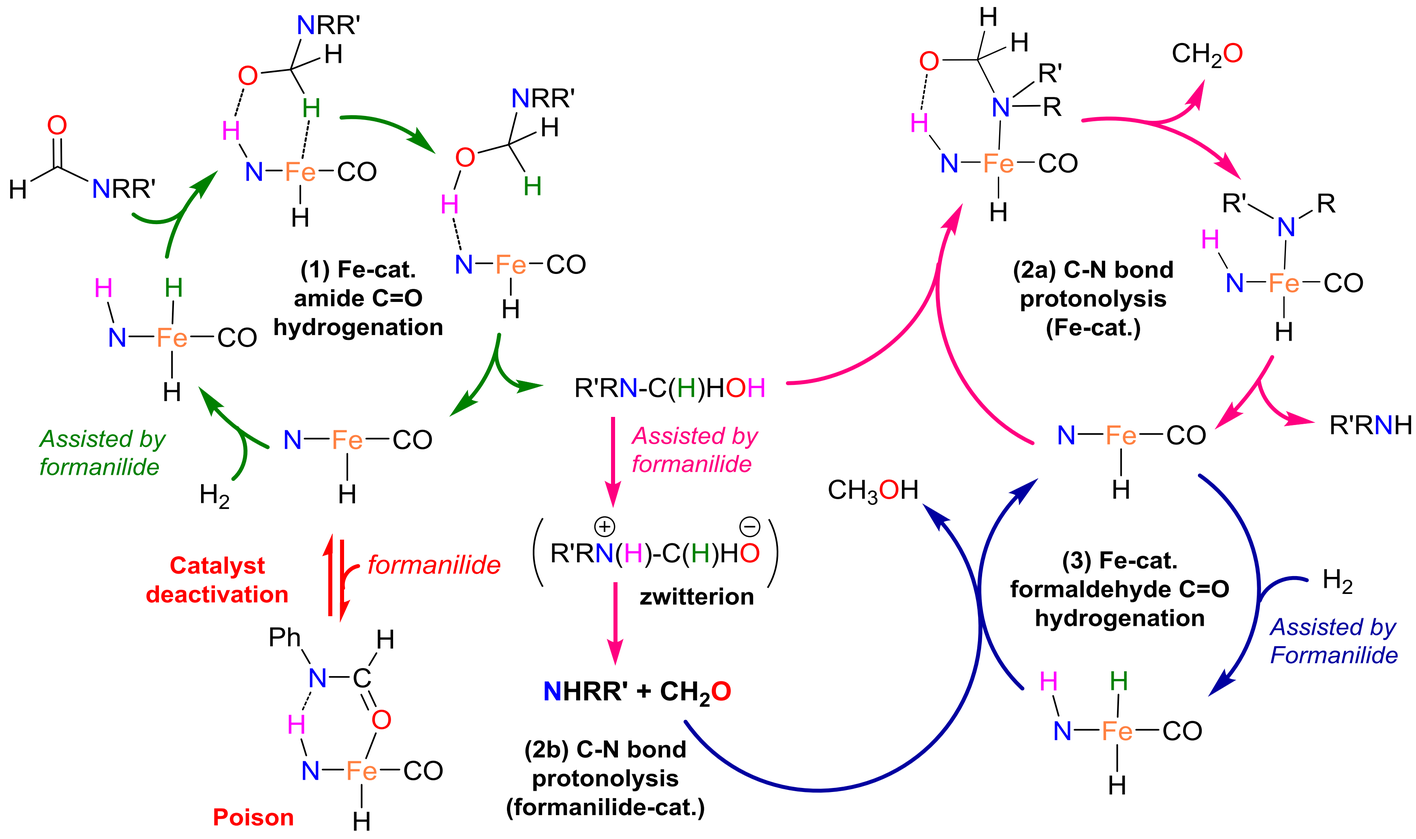
	Amide	Hemiaminal	Formaldehyde	Methanol
Formanilide	**0.0**	**4.7**	**5.2**	**-10.1**
DMF	**0.0**	**10.5**	**13.8**	**-1.5**

Figure 2. Reaction thermodynamics for the formanilide and DMF hydrogenation.

Reaction mechanism

Step 1.
The reaction starts by the hydrogenation of the amide carbonyl group. The highest energy barrier of this process is the proton transfer from the catalyst ligand to the carbonyl oxygen, which is **16.9** kcal/mol with formanilide and **23.4** kcal/mol with DMF.

Catalyst deactivation.
The adduct named **Poison**, has been crystalized when **Fe-cat** was in presence of formanilide. The higher stability of this species compared to the **Fe-cat** (ΔG = -2.0 kcal/mol) allows for catalyst deactivation.



Step 2.
The mechanism for the C-N bond protonolysis of hemiaminal is catalyzed by de-hydrogenated **Fe-cat** when derived from formanilide via pathway 2a ($\Delta G^{\ddagger}$ = **24.9** kcal/mol). With DMF-derived hemiaminal, this pathway is too high in energy (**41.0** kcal/mol). But the reaction is feasible by pathway 2b in which formanilide is used as co-catalyst (**23.6** kcal/mol) instead of **Fe-cat**.

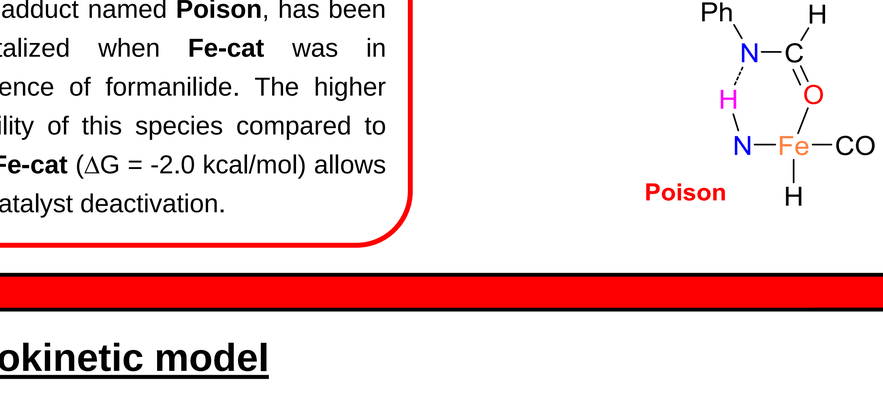
Step 3.
The hydrogenation of formaldehyde to methanol is catalyzed by the **Fe-cat**. This reaction has a low energy barrier of **5.6** kcal/mol and is thermodynamically favorable by 15.3 kcal/mol, driving the overall reaction.

Microkinetic model

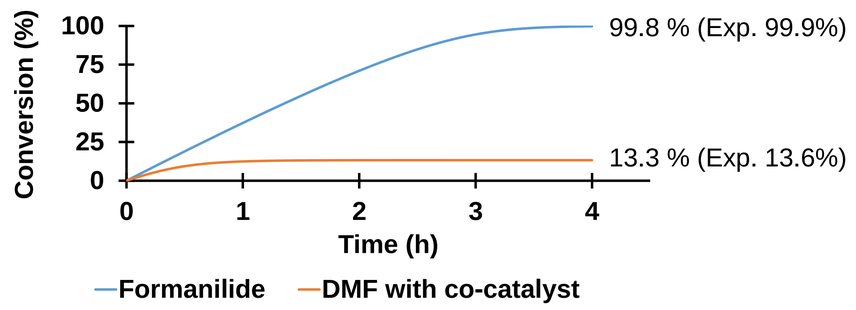
A simplified version of the mechanism was used for microkinetic modeling to study the effect of the catalyst deactivation, determine the key transition states and validate our model.

We observed that the conversion of formanilide to methanol and amine was highly sensitive to the energy barrier of **pathway 2a** and strongly correlated to the stability of **Poison** (Graph 1). The experimental conversion was only achieved when correcting -3 kcal/mol the energy barrier for the C-N bond cleavage (**pathway 2a)** and increasing 2 kcal/mol the energy of **Poison.**

When this corrections are included in the model, the calculated conversion of both formanilide and DMF match closely with the experimental data (Graph 2).



Graph 1. Conversion of formanilide after 4h and its dependence with **Step 2a** and **Poison** stability.



Graph 2. Conversion evolution over time with corrected mikrokinetic model.

Conclusions

- The mechanism for the deaminative hydrogenation of amides depends on the nitrogen substituents.
- Formanilide hydrogenation key transition state is the C-N bond cleavage and it is catalyzed by **Fe-cat**.
- DMF hydrogenation key transition state is the proton transfer and can be catalyzed by a co-catalyst that acts as a proton shuttle.
- A better catalyst for formanilide should further stabilize the amido group, while a better co-catalyst for DMF should not strongly coordinate the catalyst, nor be consumed by side reactions.
- This results give a new perspective on the stablished principle that the mechanism for hydrogenation of amides is governed by its carbonyl reduction.

Computational details: The hybrid meta-GGA M06 functional was selected on the basis of geometry and energy benchmarks, using X-Ray crystal structures and CCSD(T) (with basis set cc-pVTZ) energies as references. Geometry optimizations were performed with LANL2DZ (for Fe) and 6-31+G** (on all other elements) basis set. Gibbs energies were refined with triple-z basis set analogs. Calculations were performed taking into account the experimental conditions: 30 atm of H_2, 100 ºC, and THF solvent (SMD model). The software used was Gaussian09 (for geometries and energies) and COPASI (for microkinetic modeling).

1. U. Jayarathne, Y. Zhang, N. Hazari, W. Bernskoetter.; Organometallics 2017, 35, 409 **2**. N. M. Rezayee, D. C. Rezayee, M. Sanford, et al.; ACS Catal. 2016, 6, 6377

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