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Mechanistic investigation of the one-pot formation of amides by oxidative coupling of alcohols with amines in methanol

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ABSTRACT

The one-pot formation of amides by oxidative coupling of alcohols and amines *via* intermediate formation of methyl ester using supported gold and base as catalysts was studied using the Hammett methodology. Determining the relative reactivity of four different *para*-substituted benzyl alcohol derivatives showed that the first step of the reaction generates a partial positive charge in the benzylic position (*i.e.* by hydride abstraction), while the second step of the reaction builds up negative charge in the rate determining step. The aminolysis of the methyl ester intermediate was further investigated by means of DFT/B3LYP. The transition state structures and energies were determined for both a concerted and a neutral two-step reaction mechanism. As expected, the base-promoted two-step mechanism was found to be the most energetically favourable and this reaction mechanism was used to construct a theoretical Hammett plot that was in good agreement with the one obtained experimentally.

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1. Introduction

Formation of amides is a fundamental reaction in chemical synthesis and is used in the production of a broad range of bulk commodities, high-value fine chemicals, agrochemicals, and pharmaceuticals [1]. Amides are usually prepared by coupling of carboxylic acids and amines using a coupling reagent or by activation of the carboxylic acid. Alternative procedures include the Staudinger ligation [2], aminocarbonylation of aryl halides [3], and oxidative amidation of aldehydes [4]. Unfortunately, all these methods require the use of stoichiometric amounts of reagents, making them generally expensive and wasteful reactions [5]. In the search for a more sustainable chemical production, great efforts have been put into replacing the stoichiometric reagents with catalytic processes. This approach is not only cheaper and more environmentally friendly but also facilitates the possibility of starting from substrates other than carboxylic acids, thus paving the way for previously unavailable synthetic routes to amides [5].

In 2007 Milstein and co-workers [6] reported the first direct acylation of amines by alcohols under liberation of molecular hydrogen using a homogeneous ruthenium catalyst. Although this simple and highly atom-efficient reaction have inspired several other research

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groups to further develop this reaction [7,8], the special handling of expensive metal complexes and ligands remains a limitation that may prevent general application. In contrast, the handling of a heterogeneous catalyst is usually more straightforward [9].

Since the first fundamental studies by Bond et al. [10], Hutchings [11], Haruta et al. [12], and Prati and Rossi [13], supported gold nanoparticles have been recognised as surprisingly active and selective heterogeneous catalysts for a number of aerobic oxidations using molecular oxygen (or even air) as the terminal oxidant [14,15]. From the standpoint of green and sustainable chemistry these oxidations are attractive, because oxygen is a cheap and abundant oxidant that produces water as the only by-product.

Recently, we reported that the combination of supported gold nanoparticles and base forms an efficient and highly selective catalytic system for the one-pot synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines in methanol [16] (see Scheme 1).

In the first step of this reaction, a methyl ester is obtained by the gold-catalysed aerobic oxidation of the alcohol or aldehyde in methanol [17,18]. It is notable that in this step the methanol serves as both solvent and reactant. In the second step of the reaction, addition of amine affords the amide by base-catalysed aminolysis of the methyl ester. As the same base promotes both steps of the reaction, the oxidative coupling can be performed in a convenient one-pot procedure under mild reaction conditions (25–65 °C, atmospheric pressure). It is important to mention that this approach is conceptually different from the gold-catalysed reactions previously reported by Wang et al. [19] and Soulé et al. [20], which are



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Scheme 1. Synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold and base as catalysts.

proposed to involve the formation and subsequent oxidation of a hemiaminal intermediate to the desired amide.

To study the structure-reactivity relationship we employed the well-known Hammett methodology [21] and focused our attention on a range of *para*-substituted benzyl alcohol derivatives (see Scheme 2).

In line with previous work [22,23], the results were obtained by performing competition experiments rather than establishing absolute kinetics. There were several reasons to choose this approach. First of all, a competition experiment is more robust towards small variations in the reaction conditions and allows the reaction to be followed to relatively high conversion without deviation from linearity. Secondly, a competition experiment can be designed to investigate a different step than the overall rate-determining step. In this study, we were interested in the elementary steps of the reaction that are directly involved in the activation of the substrates. It was therefore desirable to disregard any effects from steps involving, *e.g.* activation of dioxygen.

2. Experimental study

2.1. Reaction procedure and analysis

A series of competition experiments were performed to investigate the structure-reactivity relationship of the two consecutive steps of the oxidation-aminolysis reaction. In these experiments, anisole (0.5 mmol), potassium methoxide (1.25 mmol), and methanol (50 mmol) were charged to a reaction tube together with benzyl alcohol (2.5 mmol) and either (4-methylphenyl)methanol, (4-methoxyphenyl)methanol, (4-chloro-phenyl)methanol, or (4-(trifluoro-methyl)phenyl)methanol (2.5 mmol). The reaction tubes were connected to a reaction station providing stirring, heating and dioxygen gas for the oxidative esterification (atmospheric pressure). The system was flushed with O₂ before 197 mg 1 wt% Au/TiO₂ catalyst (Mintek) was added, corresponding to an Au/substrate molar ratio of 1/500. During the following two days, samples of 0.1 ml were periodically collected, filtered, and analysed by GC-FID and GC-MS using anisol as internal standard. When all reactions had reached full conversion, hexane-1-amine (10 mmol) was added and the temperature was increased to 65 °C (reflux temperature of methanol). During the following two days additional samples were collected and analysed.





Scheme 2. Overview of the competition experiments carried out to determine the relative reactivity of the various *para*-substituted benzyl methyl esters.



Fig. 1. Kinetic plot for the first step of the reaction showing the relative reactivity of four different *para*-substituted derivatives relative to benzyl alcohol.

2.2. Results and discussion

In the first series of experiments, the conversion of all benzyl alcohols followed first order kinetics, which allowed the construction of the kinetic plots shown in Fig. 1. From these plots the relative reactivity could be determined as the slopes of the lines found by linear regression [24]. The assumption that the oxidation of all methyl esters followed first order kinetics could be justified from the good correlation coefficients ($R^2 > 0.98$).

With the relative reactivity of the four different *para*-substituted methyl esters at hand, the Hammett plot could be constructed using three distinct sets of σ -values from literature [25,26] (Fig. 2).

Fig. 2 shows that the best linear correlation of $\log(kX/kH)$ was obtained with the σ^+ -values ($R^2 = 0.922$), which resulted in a relatively large negative slope ($\rho = -0.680$). A negative slope in the Hammett plot indicates that a positive charge is built up during substrate activation, which suggests that the reaction proceeded through the generation of a partial cation in the benzylic position, *i.e.* by β -hydride elimination.

Fristrup et al. [27] have previously reported a similar result from the gold-catalysed oxidation of benzyl alcohol to benzaldehyde ($\rho = -1.10$). In that study the involvement of the β -hydride abstraction step was further confirmed by a significant kinetic isotope effect (KIE), when benzyl alcohol with deuterium incorporated in the α -position was employed as substrate. Furthermore, Fristrup et al. [28] have investigated the conversion of benzaldehyde to methyl benzoate and found here a positive ρ value ($\rho = 2.51$). These results suggest that the gold-catalysed esterification of alcohols with methanol occurs through the formation of an aldehyde intermediate and that this is the rate-determining step. The formation of an aldehyde intermediate also explains the formation of imines when the oxidation is carried out in presence of both methanol and amine [29].



Fig. 2. Hammett plot obtained using the relative reactivity determined during the oxidation of the benzyl alcohols.



Fig. 3. Kinetic plot for the second step of the reaction showing the relative reactivity of four different *para*-substituted derivatives relative to methyl benzoate.

When all the oxidation reactions had reached full conversion, hexane-1-amine was added to the reactions and data for a second Hammett study could be obtained. Also here linear kinetic plots could be constructed from the conversion of substrate, which allowed determination of the relative reactivity (see Fig. 3). The corresponding Hammett plot is shown in Fig. 4.

Fig. 4 shows that the best linear correlation was obtained with the neutral σ -values (R = 0.980), which resulted in a relatively large positive slope (ρ = 1.738). The positive slope shows that a negative charge is building up during the reaction. A Hammett study was also performed starting with pure methyl benzoate esters. As expected these experiments showed that the water formed from the oxidation of the benzyl alcohols to the methyl esters had no significant effect on the relative reactivity (see Supporting information).

Comparison of Figs. 2 and 4 shows that the effect of the substituents are opposite in the two reactions. For instance, electron withdrawing substituents decrease the reactivity in the oxidation step but increase the reactivity in the consecutive aminolysis step – and *vice versa*.

3. Computational study

3.1. DFT calculations

In order to understand the observed structure-reactivity relationship, the second step of the synthesis was modelled by means of Density Functional Theory (DFT) using the B3LYP functional [30,31] in line with earlier work [32,33]. The 6-31G** basis set [34] was applied and solvation energies calculated using the built-in PCM model [35,36] with parameters suitable for methanol [37] as incorporated in Jaguar v. 7.8 release 109 from Schrodinger Inc. [38] All structures were optimised in gas phase and characterised by computations of the harmonic vibrational frequencies at the same level



Fig. 4. Hammett plot obtained from the relative reactivity of the *para*-substituted methyl benzoates.



Fig. 5. Energy diagram for the concerted and two-step reaction mechanism, respectively.

of theory. Transition states were found to have one negative eigenfrequency, as required. Furthermore, the transition state structures were investigated by relaxation following the Intrinsic Reaction Coordinate (IRC), which lead to structures resembling pre-reactive and post-reactive complexes, as expected. Single-point solvation energies (methanol) were calculated for the structures optimised in gas phase. In order to avoid direct comparison between neutral and charged species we decided only to include neutral species in the investigated mechanisms (*vide infra*). Although recent developments have improved implicit solvation model tremendously, it is still doubtful whether a comparison between a neutral and a charged species is sufficiently accurate [39].

3.2. Results and discussion

Initially, two possible mechanistic pathways were examined for the aminolysis of methyl benzoate with ammonia [40]. In the first reaction mechanism all bond forming and -breaking interactions were assumed to occur in a single step. The transition state of this "concerted" reaction mechanism involves simultaneous C–N bond formation, C–O cleavage and a proton transfer, as shown in Scheme 3.

In the second mechanism under consideration the aminolysis was assumed to occur in two steps (Scheme 4). In the first step, a C–N bond is formed as a proton is transferred from ammonia to the oxygen atom of the C=O double bond. In the second step of the mechanism, the tetrahedral intermediate [41] is converted into benzamide and methanol by cleavage of the C=O bond, reformation of the C=O double bond, and a proton transfer between the two oxygen atoms.

The optimised structures of transition states; TS, TS1 and TS2 are shown in the supporting information together with the structure of the tetrahedral intermediate. A comparison of the relative energies, with and without a solvent model, is shown in Fig. 5.

Fig. 5 shows that the concerted reaction is predicted to be the most energetically favourable mechanistic scenario. As expected, the implementation of the solvent model results in lowering of the relative energies.

Schaefer and co-workers [40] have previously investigated the aminolysis of methyl benzoate by DFT and *ab initio* methods and proposed a model, where considerable energy savings are realised by including an additional ammonia molecule in the computations. In this model, the additional NH₃ molecule serves as an H-bridge that opens up the four-membered ring intermediate and favours the H-transfer between the hydroxylic oxygen atom and the methoxy group. The optimised transition state structures with an additional ammonia molecule are shown in Figs. 6 and 7, respectively.

Fig. 8 shows the effect of including an additional ammonia molecule in the model. Compared to the energy diagram in Fig. 5,



Scheme 3. Concerted reaction mechanism.



Scheme 4. Two-step reaction mechanism.



Fig. 6. The optimised transition state structure TS for the concerted mechanism.

Table 1

Relative energies for the *para*-substituted methyl benzoate derivatives along the two-step mechanistic pathway.

Substituent	TS1 [kJ/mol]	Intermediate [kJ/mol]	TS2 [kJ/mol]
p-CF ₃	79.4	31.3	87.0
p-Cl	82.9	34.4	100.0
p-H	88.5	37.8	104.5
p-CH₃	91.8	40.8	107.3
p-OCH ₃	95.0	44.4	111.0

the figure shows that besides stabilising the intermediate, the ammonia molecule also lowers the relative energy of the transition states. Interestingly, this effect is most profound for the twostep mechanism, which now becomes the energetically favourable mechanism. Furthermore, the figure shows that the second step of the mechanism is predicted to be rate-determining.

Fig. 8 shows how the additional ammonia molecule promotes both steps of the reaction and results in considerable lowering of the relative energies along the reaction pathway. Methanol has the same effect as ammonia, but although the first step is slightly lower in energy (4 kJ/mol) the ammonia-promoted mechanism is



Fig. 8. Energy diagram for the concerted mechanism with an additional ammonia molecule.



Fig. 9. Energy diagram showing the promoting effect of ammonia and methanol.

the most favourable when it comes to the second step (13 kJ/mol) (see Fig. 9).

In order to compare the theoretical calculations with the experimental results, the ammonia molecule was replaced with an amine. To limit the number of possible conformations we chose methylamine instead of hexane-1-amine (which was used for the



Fig. 7. The optimised structure of TS1 (left), the intermediate (middle) and TS2 (right) for the two-step mechanism.



Fig. 10. Theoretically calculated Hammett plot.

Hammett study). Table 1 compiles the relative energies computed from the transition state structures of the five *para*-substituted derivatives that were used in the experimental Hammett study.

The energies in Table 1 were used to construct the Hammett plot in Fig. 10 using the Arrhenius equation. The best linear correlation of log(*kX*/*kH*) was obtained with the σ -values (R^2 = 0.945) which resulted in a line with a relatively large positive slope (ρ = 2.855). On the other hand, poor correlations were obtained with the corresponding σ^- -values (R^2 = 0.883, ρ = 2.476) and σ^+ -values (R^2 = 0.877, ρ = 1.762).

The limitations of the B3LYP functional are well known and have been addressed earlier by adding either classical dispersion terms [42] or by using improved exchange-correlation functionals that incorporates kinetic energy–density terms [43]. However, recalculation of the relative reaction rates in Fig. 10 using the M06 functional only resulted in a slight change of the corresponding reaction constant (from ρ_{cal} = 2.856 to 2.894). As expected, these results show that the main contribution to the relative energies comes from electrostatic forces rather than dispersion forces. Compared with the experimental results described in the previous section (ρ_{exp} = 1.724), the Hammett plot in Fig. 10 has a larger slope (ρ_{cal} = 2.856). However, the resulting lines both have positive slopes in the same order of magnitude, which shows that the experiments and the model are in relatively good agreement.

4. Conclusion

The one-pot synthesis of amides was investigated in two consecutive Hammett studies. The studies were performed by competition experiments rather than by establishing absolute reaction kinetics and the investigated substrates were *para*-substituted benzyl alcohol derivatives.

The result from the first Hammett study suggested that the gold-catalysed oxidation of benzyl alcohol occurs with build-up of positive charge in the benzylic position, which corresponds to a β -hydride abstraction step. The negative slope of the Hammett plot (ρ =-0.680) was in good agreement with the generally accepted perception that the gold catalysed esterification of alcohols with methanol occurs through the formation of an aldehyde intermediate and that this is the rate-determining step.

The result from the second Hammett study showed that the reaction rate was very sensitive to the substituents and that negative charge is formed during the reaction ($\rho = 1.738$). The aminolysis of the methyl ester intermediate was further investigated by means of Density Functional Theory. The transition state structures and energies were determined for both a concerted and a neutral two-step reaction mechanism. The base-promoted two-step

mechanism was found to be the most energetically favourable route, and using this mechanism it was possible to construct a theoretical Hammett plot that was in good agreement with the experimental results. The overall good correspondence between theory and experiment gives hope for the use of DFT calculations as a predictive tool to improve the reaction protocol, for instance by calculating the relative energy barriers when using ethanol instead of methanol. Furthermore, it could be envisioned that possible additives may be screened *in silico* to avoid time-consuming and waste-producing experiments.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cattod.2012.04.026.

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