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# Reaction kinetics of rhodium catalysed hydrogenations in micellar solutions

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**Abstract**

The reaction kinetics of the rhodium-phosphine catalysed hydrogenation of methyl-(*Z*)-α-acetamidocinnamate (MAC) was studied both in micellar solutions and in methanol. A comparison shows a strong dependence of the reaction order of the substrate on the nature of the reaction media. In aqueous micellar solutions of a nonionic and an ionic surfactant the reaction rate gets zero order towards the substrate concentration, due to the stabilisation of the rhodium–substrate complex in the micelles. The reaction rate is only affected by the hydrogen insertion step. The effective activation energies give additional information about the reaction mechanism.


*Keywords:* Rhodium; Hydrogenation; MAC

## 1. Introduction

The enantioselective hydrogenation of methyl-(*Z*)-α-acetamidocinnamate (MAC) (Scheme 1) in homogeneous, multiphase, amphiphilic or micellar solutions is one of the most applied reactions in order to study the activity of homogeneous hydrogenation catalysts [1].

First mentioned in the early 1970s by Knowles et al. [2] and Dang and Kagan [3,4] the enantio- and regioselective hydrogenation of amino acid precursors with chiral rhodium–phosphine complexes attracted a great deal of attention. Not only in research but also in industrial applications like the Monsanto process established by Knowles [5] this type of reaction receives interest in many fields. The first reactions were carried out in organic solvents, namely methanol. The low solubility of the catalyst and (most) the substrates prohibited to transfer the reaction into an aqueous solution. Oehme reported significant enhancement of the reaction rate as well as the enantioselectivity of the hydrogenation of MAC in water when amphiphiles were added [6–9]. This activation is caused by the embedding of the water insoluble catalyst in the micelles. Different types of surfactants were studied [10,11] and most of them, ionic as well as nonionic and zwitterionic, promoted this effect. In the last 10 years this behaviour has been proved for many reaction systems.

The mechanism and the catalyst cycle of the hydrogenation of amino acid precursors with phosphine-activated rhodium(I)-catalysts (in this case BPPM, (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)-pyrrolidine was used as ligand) are of the Wilkinson type [12,13]. Addition of substrate and hydrogen to form an octaedric dihydride complex is followed by insertion of hydrogen into the double bond. The hydrogenated product leaves the complex and will be replaced by a new

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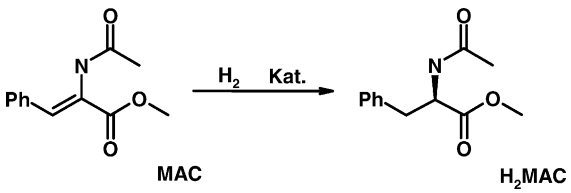
**Nomenclature**

| | |
|---|---|
| $A$ | ratio of $k_2$ and $k_1$ |
| $c_i$ | concentration of substance $i$ |
| $c_{i,0}$ | start concentration of substance $i$ |
| $E_{a,eff}$ | effective activation energy |
| $E_{a,2}$ | activation energy of the hydrogen insertion step |
| $He$ | Henry constant |
| $k_{eff}$ | effective rate constant |
| $k_j$ | rate constant of reaction $j$ |
| $K_{diss}$ | dissociation constant of the rhodium–substrate complex |
| $p_i$ | partial pressure of substance $i$ |
| $p_{tot}$ | total pressure |
| $p_0$ | normal pressure; 1.013 bar |
| $R$ | gas constant; 8.314 J/(mol K) |
| $t$ | time |
| $T$, $\vartheta$ | temperature |
| $T_0$ | normal temperature; 273.15 K |
| $V$, $V_{H_2,\Sigma}$ | integrated hydrogen volume |
| $V_R$ | reaction volume |

substrate. The catalyst cycle for the formation of the main product (*R*)-$H_2$MAC is shown in Fig. 1 [14].

Recent investigations identified the hydrogen insertion step to be the rate determining step in the overall catalyst cycle. So far, detailed reaction kinetics have been determined only for the use of methanol and other organic solvents [13–18]. In [19], a Michaelis–Menten-like reaction kinetics is suggested for the hydrogenation of dimethylitaconate with a water soluble rhodium–TPPTS complex. One advantage of micellar solutions is the embedding of the catalyst in the micelles, allowing easy separation from the reaction products by ultrafiltration. In this way, reaction and separation can be combined allowing steady-state flow processing. For sizing and construction of the steady-state flow process precise knowledge of the reaction kinetics and the behaviour of the system towards changed operating parameters is necessary.




Scheme 1. Enantioselective hydrogenation of MAC.

## 2. Experimental

All chemicals ($Rh(cod)_2BF_4$, BPPM and SDS) were purchased from Fluka–Sigma–Aldrich and used without further purification. MAC was synthesised via the known procedure [20]. The gasses (nitrogen and hydrogen) were of high purity (5.0). The micellar solutions were formed using either the ionic amphiphile sodium dodecylsulphate (SDS) or the nonionic, technical grade Marlipal O13/80, an eightfold ethoxylated $C_{13}$-alcohol supplied by Sasol Germany, Olefins and Surfactants.

The hydrogenation experiments were carried out in a 200 ml glass reactor vessel (1) equipped with a gas dispersion stirrer (2) and one buffle (Fig. 2). Isothermic conditions were ensured by the use of a thermostat (5). Reactions were performed in semi-batch mode with hydrogen being permanently fed into the reaction vessel to maintain a constant total pressure of 1.1 bar inside the reactor. The reaction progress was followed by measuring the consumption of hydrogen using a pressure controller (3) and a flow meter (4). The pressure and the hydrogen flow were analysed on a PC together with the integrated hydrogen volume.

In order to start the reaction 0.033 mmol $Rh(cod)_2BF_4$, 0.037 mmol BPPM, 2 mmol MAC and surfactant were filled into the vessel. The closed vessel was evacuated and flushed with nitrogen 8 times. Oxygen was removed from water (50 ml) by bubbling nitrogen through the dropping funnel (6) for 30 min. After this preparation the water was added into the vessel and the stirrer was started. When the reaction mixture was thermostated to reaction temperature, the stirring was stopped, the vessel was evacuated and opened to the hydrogen line. The reaction started when the stirrer was turned on again.

After the reaction was completed, 5 ml of the reaction mixture were extracted with 2 ml chloroform. The conversion as well as the enantioselectivity of the reaction were analysed from the organic phase by gas chromatography (HP 5710A equipped with a chiral Chrompack Chirasil-Val-D column, 160 °C isothermal, carrier gas $N_2$).

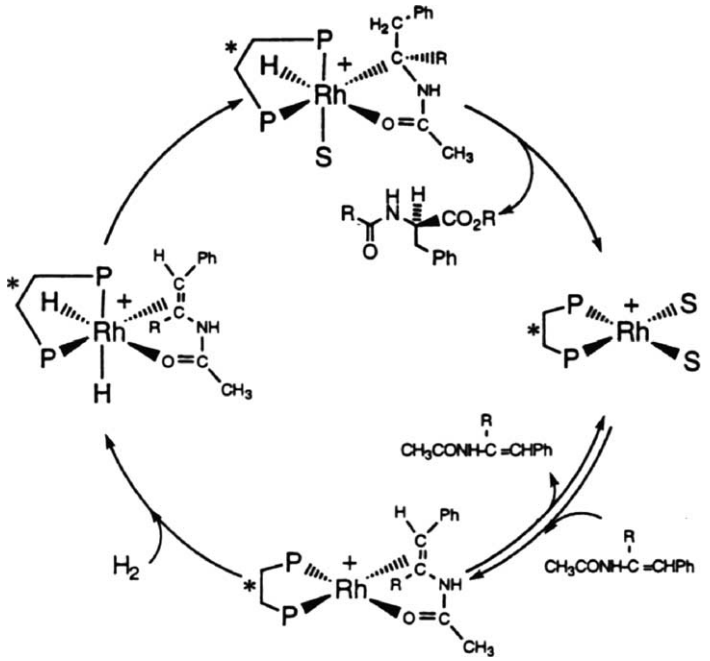


Fig. 1. Catalyst cycle for the formation of the main product (*R*)-$H_2$MAC [14].

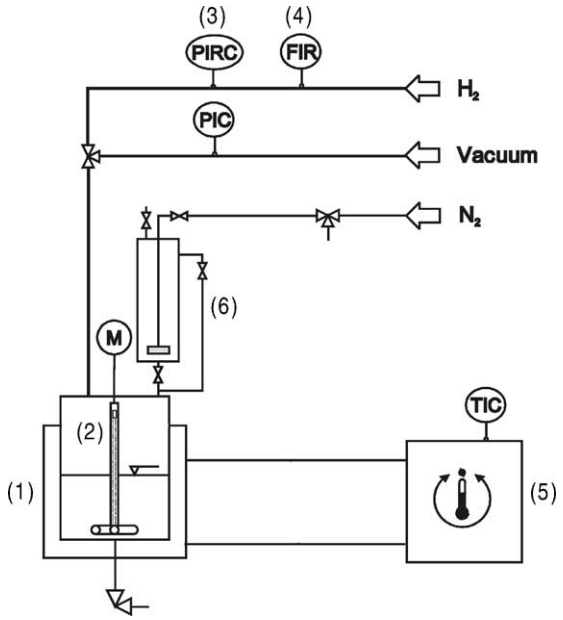



Fig. 2. Experimental set up: (1) reaction vessel, (2) gas dispersion stirrer, (3) pressure controller, (4) flow meter, (5) thermostat, (6) dropping funnel.

## 3. Results and discussion

### 3.1. Effective activation energy, $E_{a,eff}$

One of the most important aspects in describing reaction kinetics is the temperature dependence, characterised by the activation energy. In addition the activation energy is helpful to distinguish between kinetic control or mass transport limitation of the reaction. The effective activation energy of the studied reaction is different for the reaction media applied (Table 1). From the hydrogen flow at short reaction times (<3 min) the effective rate constant $k_{eff}$ was determined according to Eq. (1). The temperature dependent Henry coefficients *He* were deduced from solubility data given in [24]:

$$V_R \frac{dc_P}{dt} = \frac{dn_{H_2}}{dt} = \frac{dV}{dt}\frac{p_0}{RT_0} = V_R k' c_{cat,0} c_{H_2} = k_{eff} c_{H_2},$$

$$k_{eff} = \frac{dV}{dt}\frac{p_0}{RT_0}\frac{1}{He(p_{tot} - p_{H_2O})} \quad (1)$$

with

$$He = \frac{p_{H_2}}{c_{H_2}} = \frac{p_{tot} - p_{H_2O}}{c_{H_2}}$$

Table 1
Rate constants and activation energies for the hydrogenation of MAC in different reaction media; $k_2$, $K_{diss}$ and $A$ are evaluated for $\vartheta = 30$ resp. 25 °C, $E_{a,2}$ and $E_{a,eff}$ are calculated from rate constants between 10 and 60 °C

| System | $k_2$ (l/(mmol min)) | $K_{diss}$ (mmol/l) | $A$ | $E_{a,2}$ (kJ/mol) | $E_{a,eff}$ (kJ/mol) |
|---|---|---|---|---|---|
| Water/SDS | 13.3 | 2.62 | 0.5 | 30.8 | 33.1 |
| Water/O13/80 | 13.2 | 2.43 | 0.5 | 29.9 | 33.1 |
| Methanol | 1.9 | 7.15 | 0.09 | 14.3 | 48.8 |
| Methanol [13] | 37.8 | 0.30 | 0.06 | 31.4 | |
| Methanol [22] | | | | 31.0 | |

The Arrhenius plot of $\ln(k_{eff})$ against $1/T$ for methanol and micellar solutions is depicted in Fig. 3. In micellar solutions the effective activation energy $E_{a,eff}$ of the reaction is 33 kJ/mol for both, ionic and nonionic systems. However, methanol as solvent increases the effective activation energy to 49 kJ/mol. These activation energies indicate that the reaction is performed under kinetic control. Additionally, we worked with a stirrer speed of more than 800 $min^{-1}$ to exclude effects of transport limitation. In this range the reaction rate does not change any more with increasing stirrer speed as observed between 200 and 600 $min^{-1}$.

This behaviour shows that there is not a simple acceleration of one reaction step caused by the solvent exchange but an influence at different steps of the reaction. In methanol, the temperature dependence of the formation equilibrium of the rhodium–substrate complex affects the overall kinetics more than in amphiphilic solution.

### 3.2. Kinetic model

Experiments in different reaction media showed a strong difference in the dependence of the reaction kinetics on the concentration of MAC as depicted in Fig. 4. In methanol as well as in micellar solution the reaction is completed after about ten minutes. In methanol solutions the consumption of hydrogen shows the typical curve shape of reactions that show a dependence on the substrate concentration. In aqueous micellar solutions the reaction appears to be zero order.

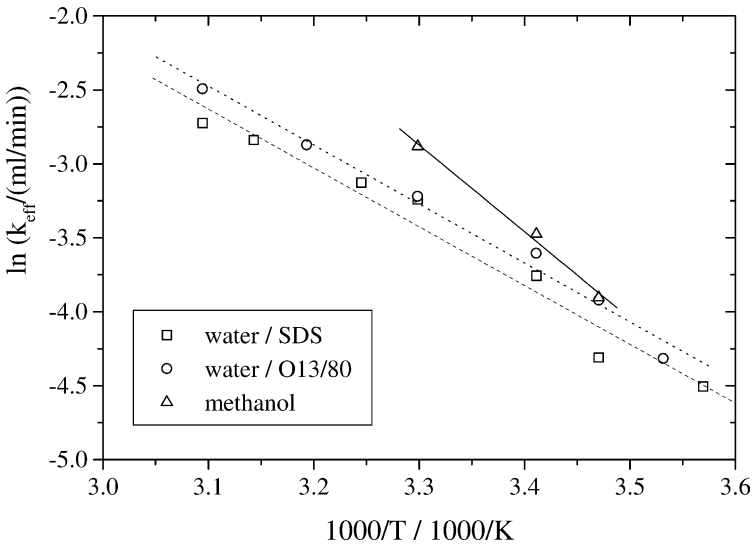



Fig. 3. Arrhenius plot for the hydrogenation of MAC in different reaction media, determination of the effective activation energy, $E_{a,eff}$.

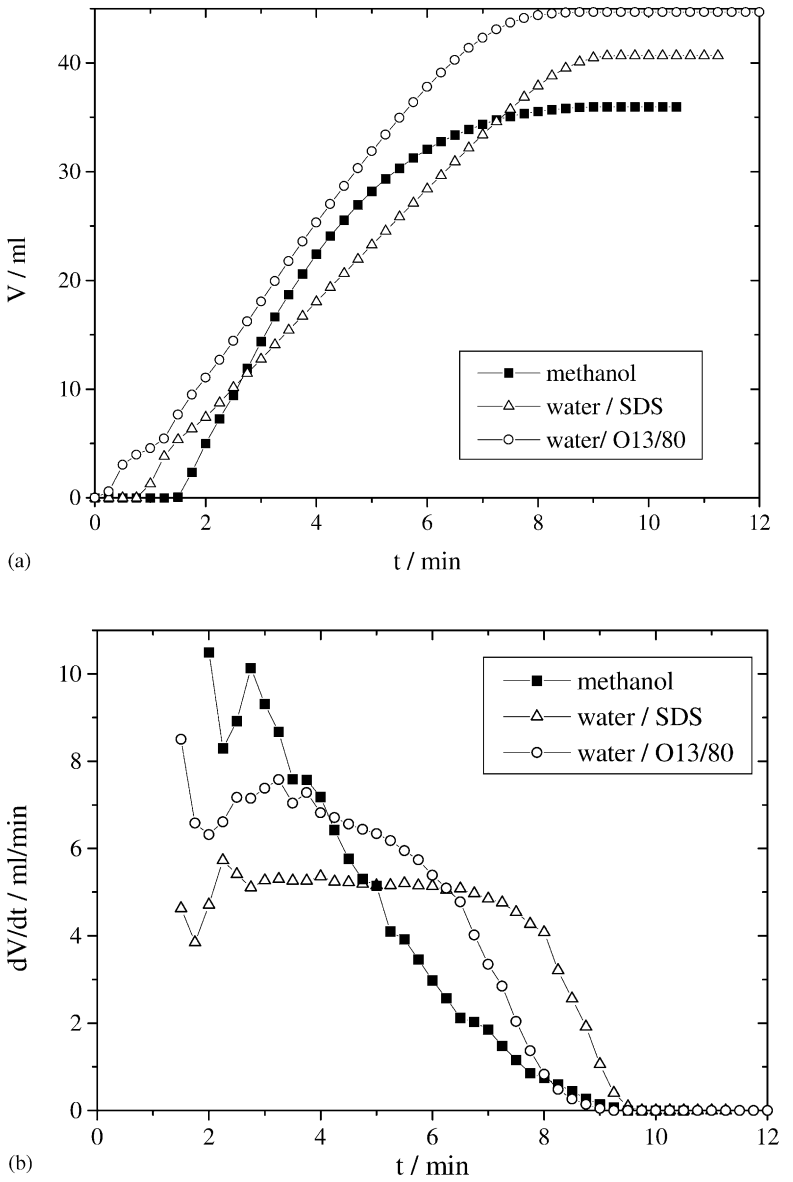
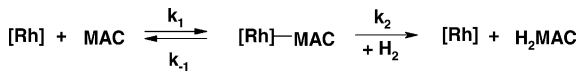



Fig. 4. Consumption of hydrogen for the hydrogenation of MAC in different reaction media: $p_{H_2} = 1.05$ bar, $\vartheta = 30\,^{\circ}$C, $c_{S,0} = 27$ up to 37 mmol/l; (a) integrated volume, (b) volume flow. The fluctuations at the beginning are caused by the behaviour of the pressure controller.

This reveals that under the conditions in methanol solutions the hydrogen insertion step which is independent on the substrate concentration is not the only rate determining step. In addition, the preliminary reversible formation of the rhodium–substrate complex has to be included in the reaction kinetics (Scheme 2).




Scheme 2. Chemical reaction scheme of the rate determining steps in the catalyst cycle.

The change of the apparent reaction order from about first to pseudo-zero order in micellar solutions indicates a stabilisation of the rhodium–substrate complex in the amphiphile layer of the micelle. According to Oehme and coworkers [21], the complex is embedded in a zone between the hydrophilic and the hydrophobic part of the amphiphiles as is the substrate. Due to this accumulation of substrate and catalyst the formation equilibrium of the rhodium–substrate complex [Rh]–MAC ($k_1$, $k_{-1}$ in Scheme 2) shifts towards the formed complex, thus the consecutive formation of $H_2$MAC ($k_2$ in Scheme 2) becomes the only rate determining step. This pre-equilibrium has a significant influence only at low substrate concentration but can be neglected at higher substrate concentrations when all catalyst molecules are engaged in rhodium–substrate complexes. This substrate dependent behaviour can be described by a rate law analogous to the Michaelis–Menten kinetics. The formation reaction of the rhodium–substrate complex is much faster than the hydrogen insertion step as shown by Landis and Halpern [13]. Its influence on the reaction rate does not derive from the kinetics but from the thermodynamic state of the equilibrium. Assuming a steady-state for the concentration of [Rh]–MAC leads to the following rate law for the formation of the main product (*R*)-$H_2$MAC:

$$\frac{dc_P}{dt} = k_2 c_{H_2} c_{cat,0} \frac{c_S}{c_S + K_{diss} + A c_{H_2}} \quad (2)$$

with

$$K_{diss} = \frac{k_{-1}}{k_1} \quad \text{and} \quad A = \frac{k_2}{k_1}$$

Herein $k_1$, $k_{-1}$ and $k_2$ are the rate constants of the reaction steps and $K_{diss}$ the dissociation constant of the rhodium–substrate complex as shown in Scheme 2.

In both reaction media the enantioselectivity was always high (ee ≥ 93%). Because of this the formation of the side product (*S*)-$H_2$MAC is not taken into account for the description of the overall reaction kinetics. With this simplification, Eq. (2) becomes identical to the rate law described in the literature for homogeneous systems [13,22].

### 3.3. Kinetic parameters

For detailed information about the individual reaction steps and to verify the assumptions made above the rate equation (2) was fitted to the measured hydrogen flows. A Nelder–Mead algorithm was used for nonlinear fitting taking the rate constant of the second reaction $k_2$ and the ratios $K_{diss}$ and $A$ as fitting parameters. The results are in good agreement with the measured data, as shown in Fig. 5 for one exemplary

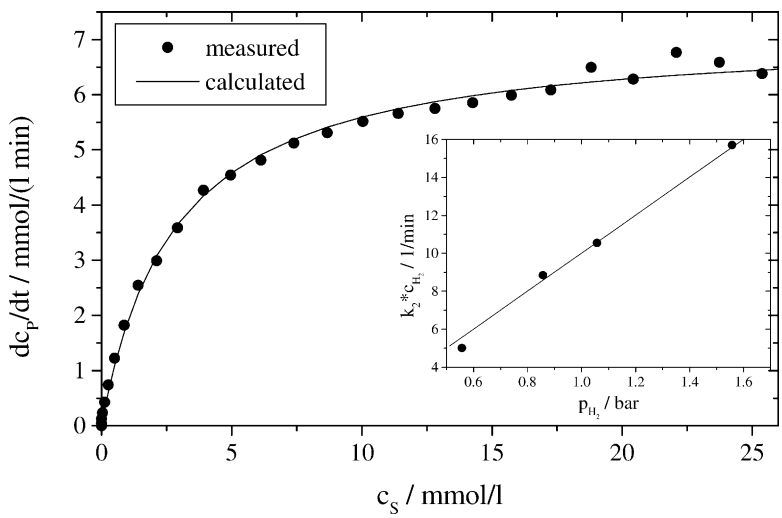



Fig. 5. Measured product formation rate as a function of the substrate concentration, the curve is calculated from Eq. (2) with the fitted parameters; hydrogenation of MAC in water/O13/80, $p_{H_2} = 1.05$ bar, $\vartheta = 30\,^{\circ}$C, $c_{S,0} = 40$ mmol/l, $c_{cat,0} = 0.67$ mmol/l. Insert: Dependence of the reaction rate on the hydrogen pressure, slope of line through origin $m = 10.0$ l/(min bar).

run. The product formation rate $dc_P/dt$ is calculated from the measured hydrogen flow. The corresponding integrated hydrogen volume leads to the substrate concentration $c_S$ by the following equation:

$$c_S = c_{S,0} - V_{H_2,\Sigma}\frac{p_0}{RT_0}\frac{1}{V_R} \quad (3)$$

Eq. (2) was not only fitted to data for different reaction media and temperatures but also to experimental data for different hydrogen pressures in the range from 0.6 up to 1.6 bar. The obtained product of the rate constant and the hydrogen concentration ($k_2 c_{H_2}$) shows a linear dependence on the hydrogen pressure (Fig. 5). This confirms that the reaction rate is first-order towards the hydrogen concentration. The reaction is kinetically controlled in the whole range of pressure.

The temperature dependence of $k_2$ yields the activation energy of the second reaction $E_{a,2}$. Table 1 compiles the results of the data fitting, the activation energies of the hydrogen insertion step ($E_{a,2}$) and the overall reaction ($E_{a,eff}$). The constants published by Landis and Halpern [13,22] for the methanol solution are also given. The deviation of $k_2$ and $K_{diss}$ from the literature data can be explained with an overestimation of the hydrogen concentration in the solution by Halpern. We can simulate his conditions by decreasing the stirrer speed and get the same results.

The dissociation constant $K_{diss}$ for the rhodium–substrate complex is significantly lower in micellar solutions than in methanol, verifying the suggested stabilisation of the catalyst complex in the amphiphile layer and the resulting shift of the equilibrium towards the complex. According to the linear dependence of the reaction rate on the hydrogen concentration the ratio $A$ is small. The influence of the hydrogen concentration in the numerator of Eq. (2) can only be seen at concentrations much higher than the ones in our experiments.

In order to discuss the rate constants $k_2$ it has to be mentioned that the saturation concentration of hydrogen in methanol is ten times higher than the one in water. Therefore the product of the rate constant and the hydrogen concentration ($c_{H_2} k_2$) has to be regarded for a comparison of the reaction rates. Looking on this product, the reaction rate in micellar solution is slightly lower than in methanol. Nevertheless, the total reaction time (time to 100% conversion) is similar in both media because in methanol the reaction is slowed down due to the influence of the pre-equilibrium.

In both micellar solutions (ionic and nonionic), the calculated activation energy for the hydrogen insertion step $E_{a,2}$ is about 31 kJ/mol, only 2 kJ/mol lower than the measured effective activation energy $E_{a,eff}$. Arrhenius' law only applies to elementary reactions, not to complex reaction systems [23]. In conclusion the effective reaction rate is only affected by the hydrogen insertion step and shows therefore the temperature dependence of this elementary reaction. The situation is different for the methanol system, where the difference between $E_{a,2}$ and $E_{a,eff}$ is significant. Here, the pre-equilibrium with its stronger temperature dependence affects the overall reaction to give a reaction rate that cannot be described by the kinetics of one elementary reaction.

## 4. Conclusions

In surfactant solutions the reaction rate is almost independent of the substrate concentration because of the stabilisation of the intermediate rhodium–substrate complex (corresponding to strong substrate binding in enzymatic systems). In contrast, in methanol the pre-equilibrium shifts to the reactant side and gets an influence on the reaction rate. Following, the reaction order of the substrate MAC increases. Fitting the rate equation (2) to the measured hydrogen consumption gives kinetic parameters that verify this effect. The dissociation constant $K_{diss}$ for the rhodium–substrate complex embedded in micelles is less than half of the one in methanol solution. The rate and the temperature dependence of the overall reaction in micellar solution is only influenced by the hydrogen insertion step. The activation energy of this reaction step $E_{a,2} =$ 31 kJ/mol is similar to the effective activation energy of the overall reaction rate, demonstrating the role of this elementary step as rate determining step. On the opposite, the activation energy of the hydrogen insertion step and the effective activation energy are quite different in methanol system. Here the overall kinetics is influenced by both steps, the formation equilibrium of the rhodium–substrate complex and the hydrogen insertion.

Based on these kinetic data it will be possible to establish a steady-state flow process with a

micellar enhanced ultrafiltration unit for catalyst recovery.

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