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Enantioselective Hydrogenation of α-Methylcinnamic Acid Over Pd/Al_2O_3: A Kinetic Study of Solvent, Temperature and Pressure Effects

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Abstract The enantioselective hydrogenation of α-methylcinnamic acid (MCA) over cinchonidine modified 5 wt% Pd/Al_2O_3 was studied in a liquid batch reactor. Both the reaction activity and enantioselectivity towards the (R) product are strongly solvent dependent. The reaction is zero order in hydrogen pressure and first order in MCA. The presence of cinchonidine does not affect the reaction order with respect to either acid or H_2 pressure, but has a significant inhibiting effect on the reaction rate. The catalyst exhibits stable activity during the reaction with no sign of deactivation.

Keywords Enantioselective hydrogenation · α-Methylcinnamic acid · $Pd/\gamma\text{-}Al_2O_3$ · Kinetic study · Heterogeneous catalyst · Semi-batch reactor · Cinchonidine

1 Introduction

Enantiopure chemicals are important in living systems, such as in amino acids, proteins and sugars, and they are important for the manufacture of pharmaceuticals, agrochemicals, and fragrances. While homogeneous catalysts are widely used in industry, intrinsic drawbacks exist, such as difficult (and expensive) catalyst separation and catalyst instability. Such issues may help to explain the relatively wide gap between R&D output from academics and industry versus commercial application [1]. In this respect, the eventual use of heterogeneous catalysts can offer several major advantages, including ease of catalyst separation, reduction of solvent usage, simplification of the synthetic route, and increased selectivity towards desired products. If optimized, these properties could result in significant economic and environmental benefits [2–7].

The first study of heterogeneous enantioselective C=C hydrogenation was apparently published in 1985 for prochiral cinnamic acid hydrogenation over Pd/C catalysts [8]. Largely over the past decade, there have been a number of studies [9–38] exploring the hydrogenation of α, β-unsaturated C=C bonds adjacent to carboxylic acid groups over Pd catalysts with cinchonidine as a chiral modifier, especially those of Nitta [9–19], Szollosi [20–23], and Baiker [24–36]. Via spectroscopic detection, the modifier cinchonidine (CD) has been shown to form a $CD(acid)_2$ complex during the enantioselective hydrogenation [31]. Based on kinetic studies, it is suggested that aromatic acid hydrogenation is favored in polar solvents, as opposed to aliphatic acid hydrogenation that is preferred in non-polar environments. However, the kinetic studies available have focused almost entirely on the final conversion and selectivity [9–23], rather than exploring kinetic parameters such as rates, reaction orders, or activation energies.

Baiker's [24–36] group has been focused on the study of *trans*-2-methyl-2-pentenoic acid, while Nitta's [9–19] group has worked on α-phenylcinnamic acid. α-methylcinnamic acid (MCA) consists of a prochiral C=C bond located between COOH and phenyl groups, and thus combines attributes of the two very well studied molecules. Bartok's group [20] discovered a small amount of benzylamine addition increases enantioselectivity of *trans*-2-methyl-2-pentenoic and α-phenylcinnamic acids, but slightly decreases enantioselectivity for MCA. Thus, MCA is an interesting model compound for enantioselective C=C hydrogenation.

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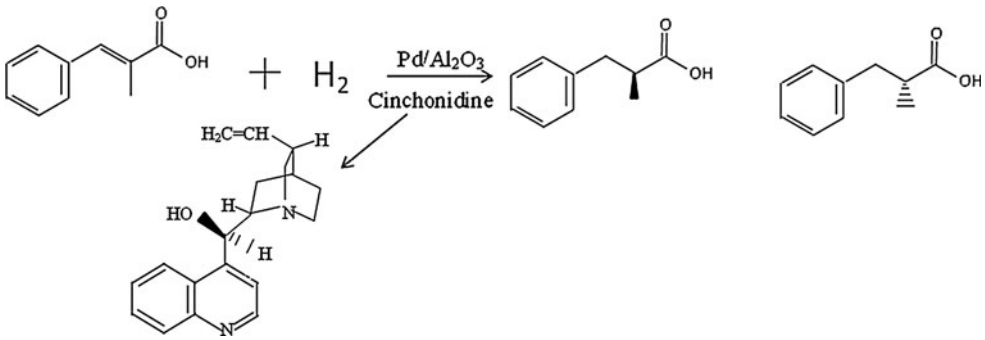

Fig. 1 Hydrogenation reaction of MCA to α-methylhydrocinnamic acid over cinchonidine-modified palladium catalyst

The present communication reports a detailed kinetic study of the hydrogenation of MCA with 5 wt% Pd/Al_2O_3 catalyst as shown in Fig. 1. Overall, the substrate has not been very well studied, with conversion and desired enantioselectivity reported to be very low over cinchonidine-modified catalysts [20, 21]. The aim of this work is to begin to study in detail, the kinetic parameters such as reaction order, activation energy and any possible product inhibition effects.

2 Experimental Section

The materials were as follows and used as received: MCA (99 %, Sigma-Aldrich), α-methylhydrocinnamic acid (MHA, 98 %, Sigma-Aldrich), cinchonidine (CD, >98 %, TCI America), dichloromethane (99.9 %, Sigma-Aldrich), isopropanol (99+ %, Alfa-Aesar), 1,4-dioxane (99.9 %, Sigma-Aldrich), N,N-dimethylformamide (Sigma-Aldrich) and 5 wt% Pd/Al_2O_3 powder (Alfa-Aesar, 14 % metal dispersion); H_2 (UHP), N_2 (UHP), and 20 % H_2/N_2 (2,000 psi) were supplied by Airgas.

Hydrogenation of MCA was carried out in a stainless steel EZE-Seal® batch reactor (Autoclave Engineers) with 100 ml capacity equipped with thermocouple, a pressure gauge and a stirring motor. In a typical reaction, the reactor was loaded with 48 ml solvent, and 0.1 g catalyst. For enantioselective hydrogenation, 0.088 g modifier (CD) was added into the reactor. After sealing, a leak check using 200 psi N_2 was performed three times, followed by three pressure/vent cycles in order to remove any residual oxygen from the system. The water-cooled stirring motor was set at a rate of 1,000 rpm based on rate measurements made at varying speeds, and was chosen to ensure that reactions were carried out free of external mass transfer limitations. H_2 was flowed for 1 h to pre-reduce the catalyst. The reaction was then initiated by an introduction of 0.97 g substrate (MCA) in 12 ml solvent solution into the reactor. In this way, the modifier/reactant ratio is fixed at ca. 1/20, which is a typical ratio for this kind of asymmetric hydrogenation [28]. The temperature of the liquid in the reactor was monitored with the thermocouple in real time during the reaction, and had a maximum deviation of 1–2 °C.

The samples collected from the reactor at different reaction times were injected automatically with a Hi-Tech 300A liquid auto sampler from Overbrook Scientific. The quantitative analysis of the product mixture was performed using a Hewlett Packard 5890 Series II gas chromatograph with a flame ionization detector (FID), equipped with a DB-1 column (15 m × 0.53 mm, J&W Scientific Inc). The ee value was determined using a CyclosilB column (30 m × 0.25 mm, J&W Scientific Inc.) after transforming the products to methyl esters. According to the literature, the (R)-product is in excess [20, 21], and the enantiomeric excess (ee) value was calculated with the equation: ee (%) = 100 × ([R] − [S])/([S] + [R]). Each experiment was repeated 3 times with error bar shown in the plots.

3 Results and Discussion

3.1 Reaction Orders in Isopropanol

Prior to examination of the solvent and temperature effects, the reaction orders for MCA and H_2 were determined in isopropanol. Several parameters were fixed for the hydrogenation reaction, including initial substrate concentration, solvent, and temperature. Both the racemic and enantioselective reactions were tested at different H_2 pressures from 1 to 30 atm. The experimental concentration versus time plots were well fitted by applying least square regression to an empirical exponential function, where a, b, and d are parameters that allowed to vary and t is time. The hydrogenation reaction rate can be expressed in a typical power law form as: $r = -\mathrm{d}C/\mathrm{d}t = kP_{H_2}^{\beta}C^{\alpha} = k_{\mathrm{app}}C^{\alpha}$. Therefore, using the differential method by plotting $\ln(-\mathrm{d}C_{\mathrm{MCA}}/\mathrm{dt})$ versus $\ln(C_{\mathrm{MCA}})$ yields the reaction order (α) and the apparent reaction constant (k_{app}) with respect to the acid substrate. As shown in Fig. 2, the MCA reaction order is ca. 1 with or without modifier in isopropanol. Similar plots were obtained for other hydrogen pressures, showing that the acid reaction order is independent of H_2 pressure.

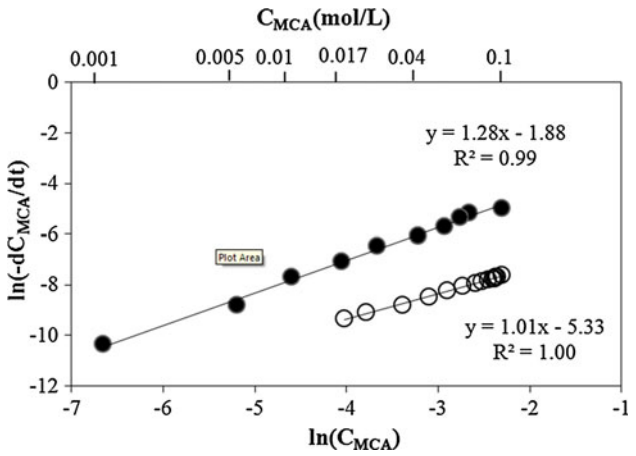

Fig. 2 Reaction order plots with respect to substrate for the hydrogenation of MCA in isopropanol in the absence (*solid circles*) and presence (*open circles*) of modifier

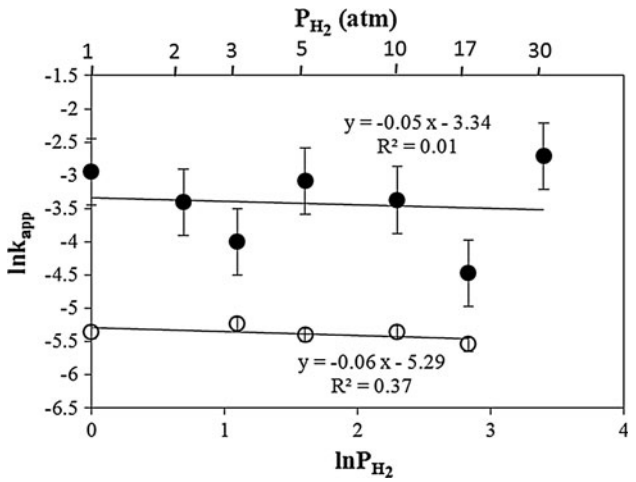

Fig. 3 Reaction order plots with respect to hydrogen for hydrogenation of MCA in isopropanol in the absence (*solid circles*) and presence (*open circles*) of modifier

Figure 3 shows further analysis by plotting ln k_{app} versus ln P_{H_2}, which allows for the evaluation of the reaction order with respect to H_2 pressure. The reaction exhibits a zero order dependence on H_2 pressure for both the racemic and modified cases. These and the previous results show that the presence of cinchonidine does not affect the reaction order with respect to either acid or H_2 pressure in isopropanol. The zero order in hydrogen suggests that hydrogen adsorption and activation is fast and equilibrated, while the first order in acid suggests that the rate determining step might be the adsorption and activation of MCA.

3.2 Solvent Effects

A summary of kinetic data obtained in various solvents is shown in Table 1. As the data indicates, this type of hydrogenation reaction is strongly solvent-dependent in terms of the activity. Among the five chosen solvents, four solvents exhibit first order in MCA, which can be explained by a Langmuir–Hinshelwood mechanism. Interestingly, the reaction is zero order in MCA in CH_2Cl_2 with or without modifier. The reason for this difference is at present unclear. For activity, isopropanol is superior, followed by 1, 4-dioxane + 1.5 vol% DI water, 1, 4 dioxane and N, N-dimethylformamide (DMF), and finally, CH_2Cl_2, which exhibits very low activity. In all cases, cinchonidine has a significant inhibiting effect on the reaction rate.

Selectivity in all these five solvents was low but clearly measurable between 5–17 %. (Table 1). Previous studies have focused on the effect of solvent polarity on enantioselectivity. Generally, the increased polarity of solvent leads to a poorer catalytic performance for aliphatic acids, while in contrast it enhances performance for aromatic acids [25]. However, the effect of solvent polarity on activity has not been extensively examined. There are several possible reasons for different activity including H_2 solubility, MCA solubility and the dielectric constant, to name a few. The solubility of H_2 in these five solvents at 298.15 K and 0.1 MPa is in the order of isopropanol > CH_2Cl_2 > dioxane > dioxane + DI water > DMF. For isopropanol, it has the highest H_2 solubility and highest activity, but for CH_2Cl_2, it has higher H_2 solubility than the other solvents but affords the lowest activity. Thus, H_2 solubility definitely will affect the activity, but it is not the main reason for these trends.

MCA solubility in different solvents was compared and found to decrease in the order of CH_2Cl_2 > DMF > dioxane > dioxane + DI water > isopropanol. This is exactly the reverse order of activity. It is reasonable because the more MCA is preferred to be in the liquid phase, the less thermodynamic driving force for MCA adsorption. This result also indicates the MCA adsorption and activation might be the rate determining step. The dielectric constant decreases in the order of DMF > isopropanol > CH_2Cl_2 > dioxane + DI water > dioxane, which does not correlate with the activity trend.

In the case of selectivity, the cinchonidine solubility in different solvents is a possible factor, and these values have been tabulated in literature [25] for DMF, isopropanol, dioxane, and dioxane + DI water as follows: DMF > isopropanol > dioxane > dioxane + DI water. However, this order does not correlate with the present findings. Another possible reason for different selectivity is the ratio between unmodified initial reaction rate and modified initial reaction rate. This ratio in isopropanol is 7, while it is 3.7 for dioxane, 4.2 for dioxane + DI water, and 3.5 for DMF. The unmodified reaction rate is much faster than the modified one in isopropanol, so the enantioselectivity is lowest, while DMF has smallest difference with highest

Table 1 Summary of kinetic results in different solvents

Solvent	Cinchonidine (mM)	Order	Conversion (%)	r_{ini} (mmol/h/gcat)	ee (%)
Isoproponal	0	1	100	185 ± 25	0
Isoproponal	5	1	97	26.5 ± 0.4	7.5 ± 0.5
Dioxane	0	1	74	52 ± 12	0
Dioxane	5	1	43	14 ± 0.6	5.5 ± 0.5
Dioxane + DI	0	1	99	68.6 ± 5	0
Dioxane + DI	5	1	70	16.2 ± 1.2	10.5 ± 0.5
N,N-dimethylformamide	0	1	83	38.2 ± 4	0
N,N-dimethylformamide	5	1	39	11 ± 1.2	17 ± 0.5
CH_2Cl_2	0	0	100	18.2	0
CH_2Cl_2	5	0	20	3	–

enantioselectivity. Addition of DI water leads to an increase in both unmodified and modified reaction rates, and the ratio between these two rates, along with a concurrent increase in the enantioselectivity. All these results suggest that not only the polarity, but also the protic character of the solvent, seem to play an important role in determining activity. In addition, enantioselectivity goes in the order of polar aprotic solvent > polar protic solvent > nonpolar solvent, which is consistent with a previous study [15]. The superior performance in polar aprotic compared with polar protic solvents might arise due the ability of the latter to disrupt the $CD(acid)_2$ complex, which is hydrogen bonded and important for the enantiodifferenting step.

3.3 TOF Calculation

To estimate the turnover frequency on modified sites from the apparent rate of reaction data obtained during the modified reaction, an analysis was performed by making several assumptions. First, the total number of sites (S) remains constant during the racemic and enantioselective hydrogenation. Second, unmodified sites (U) exhibit the same activity, whether in the absence or presence of modified sites. This assumption that modified and unmodified sites co-exist on the same metal surface is well established from the surface spectroscopic literature [39, 40]. Third, modified sites (M) exhibit a perfect selectivity, directing the hydrogenation 100 % towards the R-enantiomer. These assumptions have been used effectively in our recent previous study of enantioselective hydrogenation of alkenoic acid over Pd catalyst [41]. A series of mathematical manipulations yields the following equations:

$$\text{Racemic reaction}: r_{rac} = (S) * (TOF)_U$$

$$\text{Selective reaction}: r_R = 1/2(U) * (TOF)_U$$

$$r_S = 1/2(U) * (TOF)_U + (S-U) * (TOF)_M$$

$$r_{sel} = (U) * (TOF)_U + (S-U) * (TOF)_M$$

where r_{rac} is the initial rate of racemic reaction, r_R and r_S are the initial rate of R and S product, respectively, during the enantioselective reaction. Using these equations, the modified sites (S) can be calculated, revealing ~91 % modified sites coverage in isopropanol, 76 % for dioxane, 81 % for dioxane + DI water and 77 % for DMF.

Figure 4 shows the corresponding estimated turnover frequencies (TOF) of modified and unmodified sites. The ratio of unmodified/modified site TOF is isopropanol > dioxane > dioxane + DI water > DMF in the region of 16–130. This follows a similar trend with enantioselectivity (i.e., DMF > dioxane + DI water > isopropanol > dioxane), with addition of DI water increasing both TOF_u and TOF_m, but preferentially the latter. It suggests that the TOF difference between modified and unmodified sites is the key reason for different selectivity, since the modified coverage is high and similar in all the solvents. The implication from this analysis is that from the standpoint of balancing the activity and the selectivity, the catalyst should be carefully modified, since the high percentage and rather low

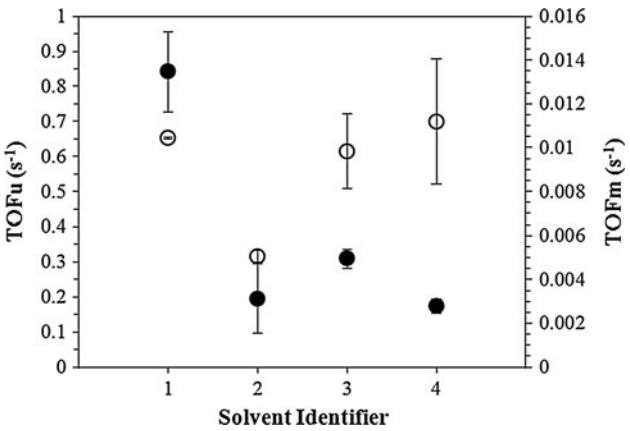

Fig. 4 Estimated TOF values for unmodified (*solid circles*) and modified sites (*open circles*) for the hydrogenation of MCA in (1) isopropanol, (2) dioxane, (3) dioxane+DI water, (4) N, N-dimethylformamide (DMF)

TOF of modified sites will result in a dramatic decrease in the overall reaction rate. It is interesting to note that this is different than the enantioselective C=O hydrogenation of a-ketoesters (and related compounds) over cinchonidine-modified Pt catalysts [42–45]. In that system, a ligand acceleration effect causes the enantioselective rates to be enhanced by at least an order of magnitude over racemic rates. Regardless of the validity of the assumptions made in the present analysis, it is apparent that such a ligand acceleration effect is not occurring in the present case of enantioselective C=C bond hydrogenation.

3.4 Activation Energy

The activation energy was calculated by using the Arrhenius equation $\ln k_{app} = \ln A - \frac{E_a}{RT}$ where k_{app} is the apparent rate constant for the reaction, A is pre-exponential factor, E_a is the activation energy for the reaction, R s the ideal gas constant in joules per mole kelvin, T is the temperature in kelvins. Plotting ln(k) versus 1/T yields $-E_a/R$ as slope. Experiments were carried out in isopropanol at 298, 306, and 313 K, with results shown in Fig. 5. For the racemic reaction (solid circles), $E_a = 44 \pm 20$ kJ/mol $= 10.5 \pm 4.7$ kcal/mol while for the modified reaction, $E_a = 45 \pm 10$ kJ/mol $= 10.8 \pm 2.4$ kcal/mol. The activation energy for the racemic and modified reactions are similar to each other, likely because of the relatively fast reaction rate on unmodified compared to modified sites, as described above (cf. Table 1). In isopropanol, the TOF for unmodified sites is 130 times faster than modified sites, so k_{app} for modified reaction is almost the same as for the unmodified reaction.

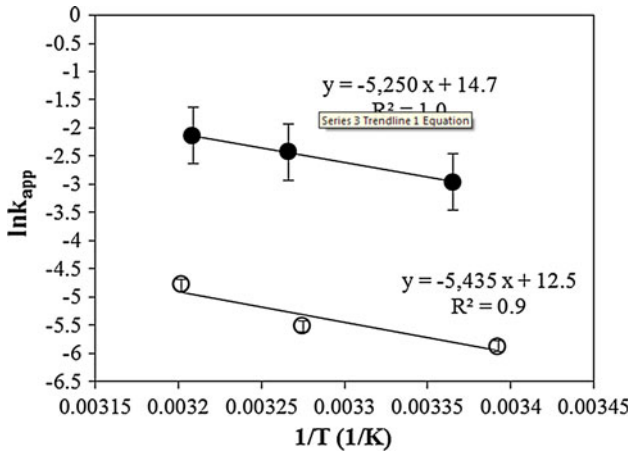

Fig. 5 Arrhenius plots obtained for hydrogenation of MCA in isopropanol solvent in the absence (*solid circles*) and presence (*open circles*) of modifier

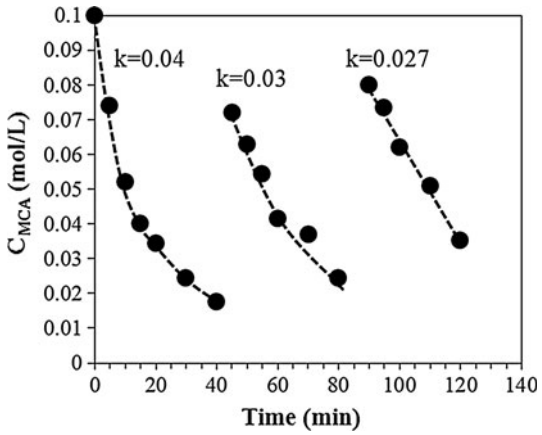

Fig. 6 Effect of adding additional reactant at various times during the hydrogenation of MCA in isopropanol. The *dashed lines* are drawn to guide the eye

3.5 Product Effect on Reaction Rate

Product desorption has been determined to be the rate determining step in several enantioselective hydrogenations [9, 14, 29, 31]. To test this possibility in the present case, two sets of experiments were carried out for the racemic reaction in isopropanol. First, the initial rate was probed with varying amounts of product injected into liquid mixture prior to the start of the hydrogenation, with other reaction conditions kept constant. For reactions with 0.1 M MCA, 0.1 M MCA + 0.1 M MHA, and 0.1MMCA + 0.2 MMHA, the initial rates of reaction are similar (185 ± 25, 186, ± 25 and 194 ± 25 mmol/h/gcat, respectively). This result suggests that the presence of product has no significant effect on reaction rate. In the second set of experiments, the effect off adding reactant over a long reaction time was examined. The reaction was run with 0.1 M MCA at the beginning, and then a certain amount of MCA was added every 40 min. The overall reaction rate constants in these three periods decreased only slightly as shown in Fig. 6. Overall, these results show the product has essentially no effect on activity for this reaction, suggesting that its possible adsorption on the catalyst surface does not compete effectively for active sites.

4 Conclusions

The kinetics of C=C bond hydrogenation in MCA over Pd/Al_2O_3 catalyst with and without cinchonidine modifier were studied in a liquid batch reactor. The hydrogenation reaction exhibits a strong solvent-dependent behavior. Regardless of the absence or presence of modifier, the reaction rate is independent on H_2 pressure and first order in the acid substrate. The TOF on unmodified sites are

much faster than modified ones, which results in the low enantioselectivity. Apparent activation energies for reaction with and without modified are similar. Finally, the product has no effect on the reaction rates or enantioselectivity, suggesting that substrate adsorption and activation may be the rate determining step.

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