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Anomalous Ligand Acceleration on Cinchona-modified Pd/C during Asymmetric Hydrogenation of Properly Substituted Phenylcinnamic Acid

Hiroyuki Ogawa, Takuya Mameda, Tomonori Misaki, Yasuaki Okamoto, and Takashi Sugimura*
Graduate School of Material Science, University of Hyogo, 3-2-1 Kohto, Kamigori, Ako-gun, Hyogo 678-1297

(Received March 21, 2013; CL-130245; E-mail: sugimura@sci.u-hyogo.ac.jp)

The hydrogenation of 4,4′-dimethoxy-α-phenylcinnamic acid over Pd/C showed a large ligand acceleration effect when a cinchonidine modifier was used; the hydrogen rate increased to 370% relative to the reaction rate on unmodified Pd/C and resulted in a 91% enantiomeric excess (ee). Another good substrate, 4-fluoro-2′-methoxyphenylcinnamic acid, also resulted in a high ee value of 92%; however, the rate increased only to 230% when this modifier was used. On the basis of the difference in the degree to which the reaction rate was accelerated, the ee_{max} for each substrate was analyzed.

The enantioselective hydrogenation of an olefin can be performed with a palladium metal catalyst in the presence of a proper chiral modifier.[1] Specially prepared Pd/TiO_2,[2] commercial Pd/Al_2O_3,[3] and pretreated specific Pd/C[4] are prominent catalysts. In addition to phenylcinnamic acid (PCA) as a standard substrate, tiglic acid[5] and substituted α-pyrones[6] are representative substrates. Cinchonidine (CD) or cinchonine (CN) is the best chiral modifier in most cases. The enantiomeric excess (ee) of the product is usually explained by two conceptually different factors. A substrate that interacts with the adsorbed chiral modifier should yield an optically active product in a certain enantiomeric excess (i%), whereas a background reaction is inevitable in heterogeneous catalysis, and part of the reaction will produce racemic products.[4] Overall, the product ee% is expressed as follows:

$$ee\% = i\% \times \frac{v_m}{(v_m + v_u)} \quad (1)$$

where v_m is the hydrogenation rate with the modifier–substrate interaction, and v_u is the rate in the absence of chiral control. The modification affects v_m both through deceleration via competitive adsorption with the substrate to decrease the adsorbed amount and through acceleration via the modifier–substrate interaction. The nature of the modifier and its amount also affect v_u through deceleration due to more extensive modification, although some unmodifiable regions will exist irrespective of the modifier concentration.

In our previous report,[7] we showed that the hydrogenation of PCA is controlled by the concentration of CN covering the Pd surface in a Langmuir adsorption equilibrium.[8] At a common modifier concentration of 2 mM, the modifier adsorption was saturated, which resulted in the highest ee ($ee_{max} = 55\%$), and the hydrogenation rate became slower than that observed with the unmodified catalyst ([M] = 0 mM). The CD modification also resulted in a slower rate under the common conditions ($v_{2mM}/v_{0mM} < 1$); however, compared with the ee_{max} achieved with the CN modification, the ee_{max} was better (82%) and the rate was decelerated to a lesser extent. Under unsaturated modifier conditions ([M] = 0.3 mM), the rate achieved with CD increased ($v_{0.3mM}/v_{0mM} = 1.3$), which indicates that ligand acceleration (hydrogenation acceleration induced by the adsorbed CD) was observed; this effect is usually obscured by the deceleration effects due to the competitive adsorption with the substrate. Ligand acceleration achieves higher catalytic activity, and more importantly, it can suppress the background non-stereocontrolled reaction due to a larger $v_m/(v_m + v_u)$ ratio (≤ 1).

For the case of CD vs. CN, the individual evaluation of factors i% and $v_m/(v_m + v_u)$ from the product ee and ee_{max} is difficult; however, such an evaluation is required for the rational improvement of the catalysis system. In this report, the factors in a CD/PCA system were examined through comparisons using two superior substrates: 4,4′-dimethoxy-α-phenylcinnamic acid (DMPCA)[9] and 4-fluoro-α-(2-methoxyphenyl)-cinnamic acid (FMPCA),[10] with which anomalous ligand accelerations were observed (i.e., $v_{0.3mM}/v_{0mM} = 3.7$ and 2.4, respectively) (Figure 1).

Hydrogenation was performed according to the reported conditions: modifier/Pd/substrate = 0.05–100/10/500 (in μmol) in 10 mL of 2.5% wet dioxane at 296 K under 10^5 Pa of hydrogen.[4] The modifier concentration corresponded to 0.005–10 mM. The reaction was completed within 3–6 h to give quantitative yields of the expected products in all experiments. The results obtained when the CD modifier was used are shown in Figure 2, and those obtained when CN was used are shown in Figure 3. The product ee% values determined by a chiral HPLC are presented in the figures in panel (a), and the relative initial hydrogenation rates (v_{xmM}/v_{0mM}) determined at 25% conversion by hydrogen consumption normalized to the corresponding rates

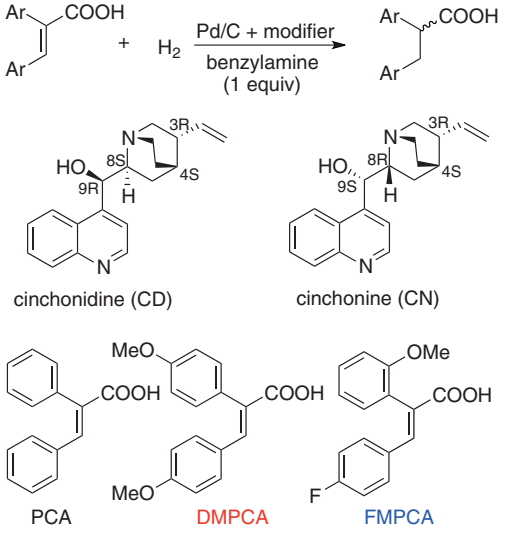

Figure 1. Enantioselective hydrogenation of α,β-unsaturated acids.

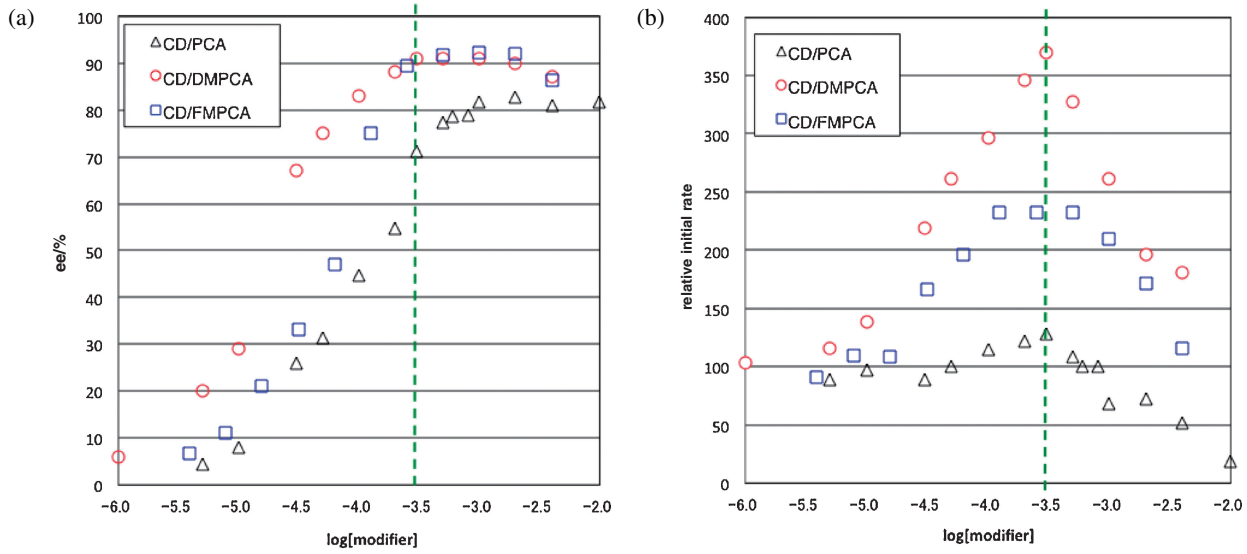

Figure 2. Product ee (left) and relative initial rate (= observed initial rate/unmodified initial rate, right) for the hydrogenation of PCA, DMPCA, or FMPCA with CD-modified Pd/C.

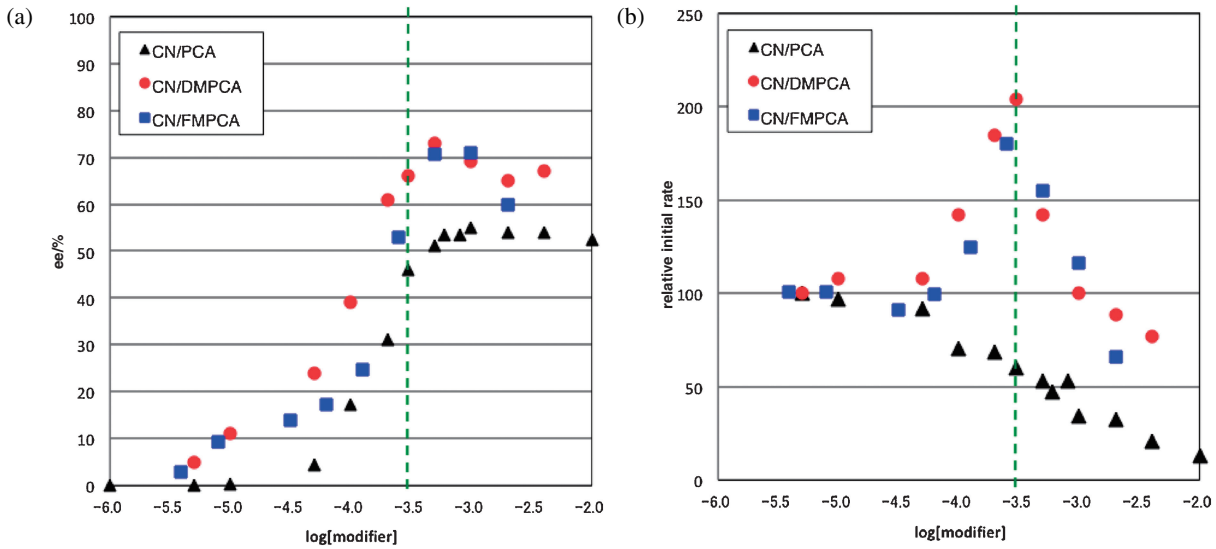

Figure 3. Product ee (left) and relative initial rate (= observed initial rate/unmodified initial rate, right) for the hydrogenation of PCA, DMPCA, or FMPCA with CN-modified Pd/C.

at 0 mM are shown in the figures in panel (b). The results for PCA are previously reported values.[7] The v_{0mM} values for each substrate were 140, 26, and 17 mmol g^{-1} h^{-1} for PCA, DMPCA, and FMPCA, respectively.

As presented in Figure 2a, both DMPCA and FMPCA showed the highest selectivity at a modifier concentration of approximately 1 mM, which resulted in high ee_{max} values of 91% and 92%, respectively. In contrast to the similar ee_{max} values, the modifier-concentration dependences were obviously different: the decrease in the ee observed with FMPCA was steeper than that observed with DMPCA at low CD concentrations. Including the result with PCA, the ee decreased in the following order: PCA > FMPCA > DMPCA. The differences in the curves shown in Figure 2a among these structurally similar substrates with the same modifier are not due to the adsorption constant of CD but can be explained in terms of the ligand acceleration, which results in a higher $v_m/(v_m + v_u)$ ratio.

In fact, obvious ligand acceleration was observed, as shown in Figure 2b: accelerations of 370% with DMPCA ($v_{0.3mM}/v_{0mM} = 3.7$) and 240% with FMPCA ($v_{0.3mM}/v_{0mM} = 2.4$) were observed. Compared with the results for PCA in the first observed example (130%),[11] the acceleration effects were obvious, and the higher $v_m/(v_m + v_u)$ ratio may explain the high ee values. The concentrations that resulted in the maximum rates were the same, which confirms that the adsorption constant of CD was unchanged in the presence of various substrates under the experimental working conditions (green dashed line). The smaller maximum rate achieved with FMPCA resulted in an ee of 92%, which is greater than that achieved with DMPCA,

Table 1. Summary of the observed data and calculated factors

Substrate	Maximum rates (no normalization)/mmol $g^{-1} h^{-1}$ (ee% in parentheses) at [modifier] = 0.3 mM			Calculated *i*% and $v_m/(v_m + v_u)$ to give ee_{max} (in parentheses)		
	CD	CN	Unmodified	*i*% with CD(ee_{max})	*i*% with CN(ee_{max})	$v_m/(v_m + v_u)$ with CD at 1 mM
PCA	180 (71% ee)	84 (42% ee)	140	82–89% (82%)	58–73% (55%)	1.00–0.92
DMPCA	96 (91% ee)	53 (66% ee)	26	96–98% (91%)	72–77% (73%)	0.95–0.92
FMPCA	40 (89% ee)	31 (53% ee)	17	96–100% (92%)	58–66% (71%)	0.96–0.92

which indicates a greater contribution of the non-stereocontrolled reaction.

The greater $v_m/(v_m + v_u)$ ratio and the lower *i*% for CD/DMPCA compared with those for CD/FMPCA reveal that CD/DMPCA contains more space for *i*% improvement and that CD/FMPCA provides a greater *i*% by compensating the v_u contribution. This result concludes that the CD/PCA system, which results in an 82% ee, can be improved through improvements in both factors. *i*% is expected to decrease with a decrease in the reaction temperature. Experimentally, 91% ee was achieved with the CD/PCA system at 288 K.[2b]

The PCA reaction with CN is expected to proceed under adsorption properties similar to those of CD/PCA. The maximum ee of 55% was improved to 73% with DMPCA and 71% with FMPCA, and the ligand accelerations were 210% and 180%, respectively. These results represent the first observation of ligand acceleration with a CN-modified Pd catalyst.[11] Although the ligand accelerations in Figure 3b between CN/DMPCA and CN/FMPCA are similar, the portion of the curve in Figure 3a with a negative slope indicates that the acceleration with DMPCA is greater than that with FMPCA. The greater degree of acceleration, which resulted in a moderate 71% ee with CN/FMPCA, indicates that the CN modification results in a lower *i*% than that achieved with CD.

The observed ee% and rates are extracted in Table 1 (see also Supporting Information).[8] The ranges of *i*% were calculated for each substrate from eq 1 using the ee% and the rate at a modifier concentration of 0.3 mM relative to the maximum rate conditions. Under the presently and commonly employed assumption, the ee values of CD/DMPCA and CD/FMPCA are improved primarily due to the improved *i*% relative to that of PCA.

The high *i*% values for the reactions with CD modifier prompted us to propose a new enantiodifferentiation model.[12] The models were usually illustrated as an adsorbed molecule on the wide bulk metal surface. Ordered modifier adsorption participating multimolecules was often proposed to explain the strict enantiorecognition.[1] However, currently employed Pd/C is a highly dispersed type catalyst (Pd dispersion = 76%);[13] small Pd particles with a mean diameter of 1.4 nm may be buried in the active carbon support, and only a part of the particle surface can adsorb the molecules participating in the reaction. Hence, the size and shape of the free Pd surfaces are limited, and most probably, a certain one-to-one complex is allowed to form at the reactive and stereoselective reaction field. Figure 4 illustrates a new model showing the adsorption of one properly interacting CD–PCA "surface salt." We are currently investigating the effects of the substituent on both the substrate and the modifier using this model.[14]

In conclusion, an obvious ligand acceleration effect was observed for DMPCA and FMPCA. On the basis of these effects, the ee values were analyzed in terms of the intrinsic stereoselectivity (*i*%) and the heterogeneity of the modification ($v_m/(v_m + v_u)$). Contrary to our expectation that the acceleration leads to high ee values through a suppression of the formation of the background racemic product (v_u), its effect was limited because $v_m/(v_m + v_u)$ was already high when PCA was used. A structural model that explains the high intrinsic stereoselectivity was also presented.

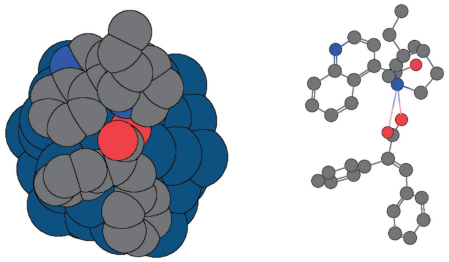

Figure 4. Expected interaction between CD and PCA on Pd metal nanoparticles with a diameter of 1.4 nm (left). The CD–PCA complex was extracted from the left figure to the right figure.

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14 General relationship between % ee and hydrogenation rate is not clear now. Since relationship between the substrate structure and the reaction properties itself is not simple, many more examples are required to clarify this issue.

