

Acceleration of Enantioselective Hydrogenation of Olefins over Pd/C by Cinchonidine as a Chiral Modifier. Comparison with Cinchonine, Pseudoenantiomer

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The performance of cinchonidine (CD) and cinchonine (CN) as chiral modifiers in enantioselective hydrogenation over Pd/C were compared in different concentrations. The catalytic hydrogenation with CD always occurred in better ee and at faster rate than that with CN. The difference is not attributable to the adsorption properties of the modifiers, but to the intrinsic enantio differentiation that accompanies the reaction acceleration.

Cinchonidine (CD) and cinchonine (CN) are enantiomeric at the 8 and 9 positions, but have the same configurations at the 3 and 4 positions (Figure 1). They are popular in asymmetric syntheses as chiral ligands or chiral organocatalysts, and usually give antipodes of the product since the 3-vinyl group does not play a major role during the chiral recognition of the substrate.¹ Both CD and CN could be also used for chiral surface modification of supported metal catalysts,² and asymmetric catalyses have been developed with Pt, Rh, Ru, Ir, and Pd catalysts. When the modified Pd catalyst is used for the hydrogenation of phenylcinnamic acid (PCA),³ CD gives higher product ee than CN, while CN provides better selectivity in the hydrogenation of substituted α -pyrones.⁴ Although the CD/CN-modified Pd catalysts have been intensively studied from a variety of viewpoints, no systematic study comparing CD and CN has been reported. Comparison of these chiral modifiers in hydrogenation of PCA revealed an acceleration effect by the modifier (ligand-acceleration effect)⁵ as an apparent and essential difference between the two modifiers.

The optimized procedure for the hydrogenation of PCA with CD modifier is as follows. A commercial 5% Pd/C (23 mg, STD

type, N.E. Chemcat) is pretreated at 353 K under H₂, and then mixed with CD (20 μ mol) in dioxane containing 2.5% water at 296 K.⁶ With this modified catalyst, PCA (0.5 mmol) in the solvent (10 mL) is fully converted to the saturated acid within 2–3 h under atmospheric hydrogen. The CN modification was performed just by replacing CD with CN. The catalytic activity was estimated by the hydrogen consumption at around 25% conversion and the stereoselectivity was evaluated by product enantiomer excess (ee) determined by chiral HPLC.

The difference between CD and CN was investigated by systematically changing solvent, temperature, Pd support, and pressure. The ee values with CD varied, but the ee with CN was always lower than CD to give the ee ratio in a range of 1.5–2.1. The CD-modified catalysts are more active than the corresponding CN-modified catalysts (see Supporting Information¹¹). Selected results are given in Table 1. The results indicated that the optimized conditions with CD were also suitable for the reaction with CN, suggesting a common stereocontrol mechanism among the modifiers.

Important phenomena were observed in the modifier-concentration dependence. The ee values obtained with the modifier in a concentration from 10⁻⁵ to 10⁻² mol dm⁻³ are given in Figure 2a. The observed initial rates are converted to the relative rates standardized by the unmodified catalysis,⁷ and are given in Figure 2b. The ee profiles for the modified reactions with CD and CN are very similar,⁸ largely constant above 0.5 mM, while decreasing below 0.5 mM maintaining a difference of 26–29% until the ee induced by CN reaches zero. The ee decrease occurring at the same concentration of modifier suggests that the adsorption constants governing concentration of the ee saturation are comparable with each other. The main factor governing the ee difference between the two modifiers must be the intrinsic stereocontrollability of the adsorbed modifier. However, the ee at the low concentration (<10⁻⁴) are not proportional indicating that the difference is not simply due to the intrinsic stereocontrollability, but CD has an extra advantage under insufficient surface modification.

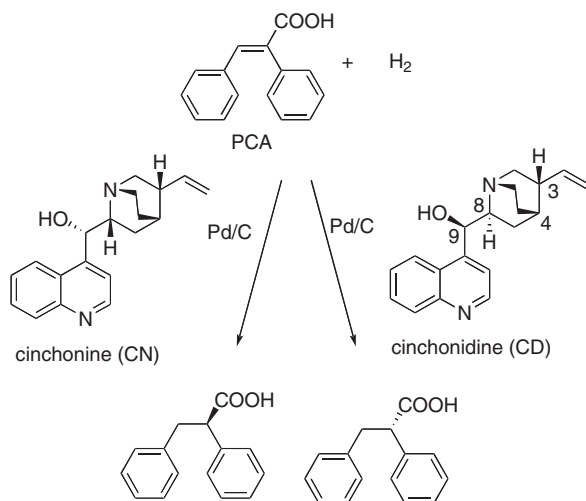


Figure 1. Configurations of cinchona alkaloids and the hydrogenation using Pd/C modified with them.

Table 1. Enantiomer excess (%ee) of the product and initial hydrogenation rate (r_0 /mmol g⁻¹ h⁻¹)

Entry	Conditions	CD		CN	
		%ee	r_0	%ee	r_0
1	Optimized for CD ^a	82.6	102	53.9	45
2	5% Pd/Al ₂ O ₃	72.7	73	33.9	31
3	1% Pd/C	61.7	23	30.7	11
4	in MeOH	52.9	51	36.8	45
5	in MeOH at 273 K	74.4	19	48.4	13
6	DMPCA ^b	90.2	51	72.8	27
7	MCA ^c	51.4	108	24.0	72

^aThe hydrogenation of PCA was carried out with 5% Pd/C in dioxane containing 2.5% water at 296 K. ^bSubstrate: *p,p'*-dimethoxyphenylcinnamic acid. ^cSubstrate: methylcinnamic acid.

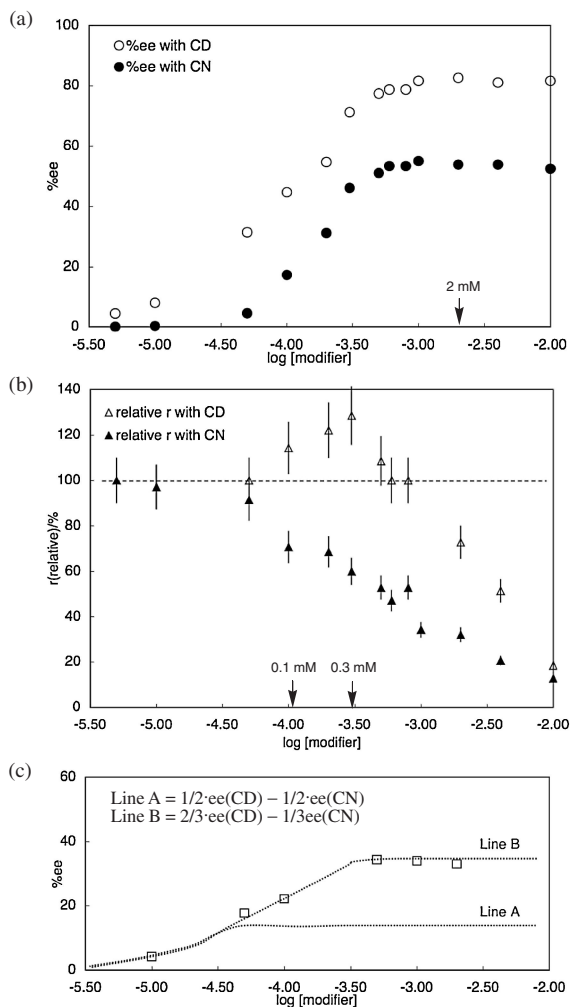


Figure 2. Hydrogenation of PCA over Pd/C modified with different concentration of CD or CN. (a) Product ee after 100% conversion. (b) Hydrogenation rate at ca. 25% conversion given as the relative rate (%) standardized by the rate with the unmodified catalyst. (c) Observed and expected ee with the CD/CN comodified catalyst.

Activity of the Pd catalyst for hydrogenation is known to be suppressed by CD-modification.^{8,9} As expected, hydrogenations are slower at the standard or higher modifier concentrations (≥ 2 mM), where the degree of suppression is smaller with CD than CN. Since the adsorption constants of CD and CN should be similar to each other, the rate difference is attributable to the difference in kinetic effects of the chiral modifier. In this context, the rate ratio of the chiral modified specific area should be $\text{CD}/\text{CN} = 2.1\text{--}2.4$. It should be noted that the rates modified with CD at 0.1–0.3 mM are even faster than the unmodified catalysis. The observed rate increment is ca. 30%, and this is the first observation of the acceleration by the CD-modification of Pd catalyst. The rate acceleration should originate from the substrate interaction with the modifier.¹⁰

The observed properties were confirmed with a comodified catalyst prepared with a 1/1 mixture of CD and CN. Figure 2c shows the ee dependency on the total modifier concentration. Dotted line A is an expected curve using the data in Figure 2a assuming that CD and CN modified the Pd surface evenly under

the reaction conditions, and the catalytic activity of the chiral modified area is the same. Line B is drawn under the same assumption except for the catalytic activity, which is 2 times faster with CD than with CN. The experimental results reasonably fit the latter presumption.

In this report, the acceleration effect by the modifier was observed for the first time in the Pd-catalyzed reactions. The acceleration effectively maintains ee when chiral surface modification is incomplete and the nonenantioselective hydrogenation over the unmodified surface competes. Since both the intrinsic stereocontrollability and the activity of the chiral modified area are better with CD than with CN, the CD modification results in better ee than CN irrespective of the catalysis conditions.¹¹ It is concluded that the difference between CD and CN is not due to the adsorption properties, but due to the intrinsic stereocontrollability and the acceleration effect, both of which originate from the interaction between the modifier and substrate.

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- The rate acceleration should occur with other substrates, but the appearances largely depend on their adsorption properties. For example, DMPCA is known to show smaller deceleration effect by the CD modification (Ref. 6), and the rate with 2 mM CD ($51 \text{ mmol g}^{-1} \text{ h}^{-1}$) is already faster than the unmodified catalysis under the present definition ($26 \text{ mmol g}^{-1} \text{ h}^{-1}$).
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.