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Kinetic analysis of the asymmetric hydrogenation of (*E*)-2,3-diphenylpropenoic acid over cinchonidine derivative-modified Pd/C: quinoline ring modification†

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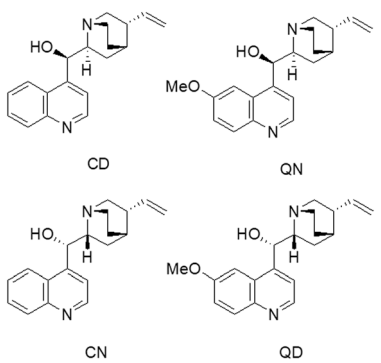
The effects of the quinoline ring modification of cinchonidine (CD) on the enantioselectivity of the asymmetric hydrogenation of (*E*)-2,3-diphenylpropenoic acid over chirally modified Pd/C were systematically analyzed from the kinetic points of view. The substitutions at the 2′- and/or 6′-positions of the quinoline ring of CD by a methyl, vinyl, *n*-butyl, or phenyl group decreased enantioselectivity over the whole range of the modifier concentration. Kinetic analysis allowed us to estimate the intrinsic enantioselectivity at modified sites and adsorption strength of the modifier. It is revealed that the substitutions reduce both the intrinsic enantioselectivity and adsorption strength of the parent modifier. The intrinsic enantioselectivity is correlated, most likely, to the modifier–substrate interaction strength.

Introduction

Enantioselective hydrogenations of α-ketoesters and α,β-unsaturated carboxylic acids over cinchona alkaloid-modified platinum and palladium metal heterogeneous catalysts, respectively, have received extensive attentions because of their pivotal significance in the molecular recognition catalysis bestowed on a chirally modified metal surface as well as in the feasibility of industrial applications.[1–10] Spectroscopic and theoretical investigations, coupled with molecular design approaches, have been extensively conducted, in particular, with chirally modified platinum catalysts to obtain deeper insights into the enantiodifferentiation mechanism[11–20] and to extend the scope of the substrates.[1,6,21–24] Much less attention, however, has been paid to their palladium counterparts.[1,6,19,20,25–30] Despite the syntheses of artificial modifiers and cinchona alkaloid derivatives by several research groups,[1,2,6,31–37] naturally occurring cinchona alkaloids, cinchonidine (CD), cinchonine (CN), quinine (QN), and quinidine (QD), have been the most effective modifiers to yield even almost complete enantioselectivity with specified modifier–substrate combinations (Scheme 1).[21–24,28–30] Extensive efforts have been devoted to understand the nature of a chiral pocket which is formed by a modifier adsorbed on a metal surface to accommodate the substrate and thereby to form enantiodifferentiating modifier–substrate interaction intermediates, thus inducing surface chiral recognition.[1–10]

The geometrical features of the adsorbed modifier define the configuration of the chiral pocket and, thereby, the energetics and dynamics of pro-*R* and pro-*S* modifier–substrate–metal surface intermediates, consequently elucidating intrinsic enantioselectivity at the modified sites.[1,2,5–7] The molecular structure of cinchona alkaloids is composed of three parts: a quinuclidine base, quinoline ring, and hydroxy-substituted stereogenic carbon linkage at C9 connecting them.[1,2,5,6] It has been revealed from experimental and theoretical studies that these molecular parts play crucial roles as chiral modifiers to define the selectivity and reaction rate in the enantioselective hydrogenations over platinum and



Scheme 1 Molecular structures of the modifiers frequently employed for the enantioselective hydrogenations over platinum and palladium metal catalysts. CD; cinchonidine, CN; cinchonine, QN; quinine, and QD; quinidine.

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palladium metal catalysts. The quinoline ring anchors the cinchona molecules on the metal surface through adsorption *via* π-electron and/or N-lone pair electron interactions with the metal surface. The N-atom of the quinuclidine moiety interacts with a substrate molecule through N–H–O hydrogen bond interactions and constitutes the chiral pocket together with the OH group attached to C9 of the linker part. The stereogenic configurations of C8 and C9 define the sense of enantioselectivity in the asymmetric hydrogenations over cinchona-modified novel metal catalysts.[1,2,5–7]

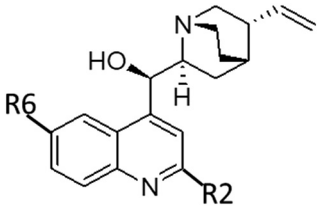
Aiming at performance improvement of the modifier and at better understanding of the reaction mechanisms, molecular design approaches have been applied to find the effects of the modifications of the quinuclidine moiety[33,38,39] and C9-hydroxy group,[12,38–47] combined with spectroscopic and theoretical approaches. However, the effect of the modification of the quinoline ring has rarely been investigated with both platinum and palladium metal catalysts for the asymmetric hydrogenations of C═O and C═C bonds, respectively, in spite of its crucial influence on the adsorption strength and geometry, which are expected to result in conformational alterations of the chiral pocket.[40,41,48,49] Comparing CD and QN or CN and QD, Huck *et al.* have shown that the substitution of the 6′-position of the quinoline ring with a methoxy group weakens the adsorption strength of the modifier on platinum[41] and palladium[40] metal surfaces, accompanying a decrease in the enantioselectivity.[1,6,38,40,41] Bürgi *et al.*[48] have found a considerable decrease in enantiomeric excess (ee) by the phenyl-substitution at the 2′-position of the quinoline ring of 10,11-dihydrocinchonidine (HCD) over a platinum catalyst for the asymmetric hydrogenation of ethyl pyruvate in acetic acid. We have previously demonstrated that the introduction of OH at the 6′-position of the quinoline ring of CD does not affect the performance of the modifier for the enantioselective hydrogenation of (*E*)-2,3-diphenylpropenoic acid (α-phenylcinnamic acid, PCA) over Pd/C.[49] In the present study, we systematically examined the effects of the substitutions at the 2′- and/or 6′-positions of the quinoline ring of CD (Scheme 2 and Table 1) on the enantioselectivity of the asymmetric hydrogenation of PCA over cinchona-modified Pd/C (Scheme 3).

It is conceivable with asymmetric hydrogenation over chirally modified platinum and palladium metal catalysts that the performance of the modifier is elucidated by the adsorption strength of the modifier, intrinsic enantioselectivity at the modified sites, modifier–substrate interaction mode and interaction energy, and reaction rate constant at the modified sites relative to that at unmodified sites. These characteristics of the modifier are reflected on reaction kinetic parameters. In consequence, kinetic approaches are expected to describe the effects of the structural modification of the modifier on the enantioselectivity as the changes in kinetic parameters. Reaction kinetic approaches contribute to understanding reaction dynamics and mechanisms, thereby providing reasonable bases for improving the catalyst performance and for industrial applications. However, kinetic approaches of heterogeneous asymmetric catalyst systems are unfortunately very limited.[7,8,50–56] In addition, these kinetic studies were usually too complicated with many undetermined parameters or too simple to include the desired information. Recently, we have developed a simple but informative reaction model and formulation to evaluate the performance of cinchona alkaloid-modified Pd/C for the enantioselective hydrogenations of α-phenylcinnamic acids.[57] We analyzed herein the enantioselectivity of a Pd/C catalyst modified with a chiral cinchonidine derivative by applying the kinetic model and formulation for the hydrogenation of PCA as a representative substrate to better understand the decisive reaction parameter(s) for the catalyst performance. Cinchonidine (CD) was substituted at the 2′ and/or 6′ positions of the quinoline moiety to modify the features of the modifier.

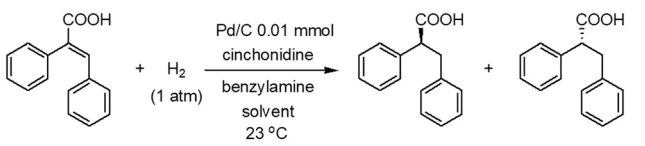
It was shown in the present kinetic study that the enantiomeric excess (ee) was decreased over the whole range of modifier concentration by the substitution at the 2′ position of the quinoline moiety of CD with a methyl, vinyl, *n*-butyl or phenyl group. It was found that the adsorption strength of the modifier was decreased by the substitution, while the adsorption strength of QN (CD substituted at the 6′ position by a methoxy group) was not affected further by methyl-substitution at the 2′ position. The intrinsic enantioselectivity at the modified sites was estimated by

Table 1 Cinchonidine derivatives used as a modifier for the enantioselective hydrogenation of PCA over Pd/C

Modifier	R2	R6
CD	H	H
CD–Me	Methyl	H
CD–Vinyl	Vinyl	H
CD–*n*-Bu	*n*-Butyl	H
CD–Ph	Phenyl	H
QN	H	Methoxy
QN–Me	Methyl	Methoxy
CD-6′OH	H	OH



Scheme 2 Schematic illustration of the cinchonidine derivatives used as a modifier for the enantioselective hydrogenation of PCA over Pd/C.



Scheme 3 Enantioselective hydrogenation of PCA over cinchonidine derivative-modified Pd/C.

kinetic analysis. It is suggested that the decrease in the intrinsic enantioselectivity by the substitution is most likely correlated to the decrease in the interaction energy between the substrate and modifier due to the change in the adsorption geometry of the modifier.

Results and discussion

The enantioselective hydrogenation of PCA was carried out over Pd/C modified with a CD derivative by the use of a batch reactor under atmospheric pressure of H_2 as reported previously.[49,57,58] With the modifier used herein, the *S*-enantiomer was the main product regardless of the modifications. Fig. 1 shows the enantioselectivity, as expressed by enantiomeric excess (ee%), and the reaction rate, as normalized by the rate without the modifier but in the presence of benzylamine (BA), as a function of $\log C_M$ (C_M: modifier concentration, mol L^{-1}) for the PCA hydrogenation over CD–Me and CD–*n*-Bu-modified Pd/C together with those over CD–Pd/C[49] for comparison. The enantioselectivity of PCA sigmoidally increased as $\log C_M$ increased, regardless of the modifier, as reported previously for cinchona alkaloid-modified palladium catalysts.[49,57–59] Fig. 2 and 3 illustrate two sets of experimental results for CD–vinyl and CD–Ph and CD-6′OH and QN–Me, respectively, together with those for CD and QN[49] for comparison. It is likely that the vinyl-group of the quinoline ring is readily hydrogenated to an ethyl group.

The maximum ee values (ee^{max}) of the CD derivatives, attained in the present study, are summarized in Table 2. It is obvious that ee^{max} is reduced by the substitution at the 2′- and/or 6′-positions of the quinoline ring of CD, depending on the substitution group in the order CD > CD–Me ~ CD–vinyl > CD–*n*-Bu > CD–Ph for the 2′-substitution and CD ~ CD-6′OH > QN > QN–Me for the 6′- and 2′-substitutions. The observed decrease in the enantioselectivity by the phenyl-substitution at the 2′-position of the quinoline ring of CD agrees with the observation by Bürgi *et al.*[48] for the

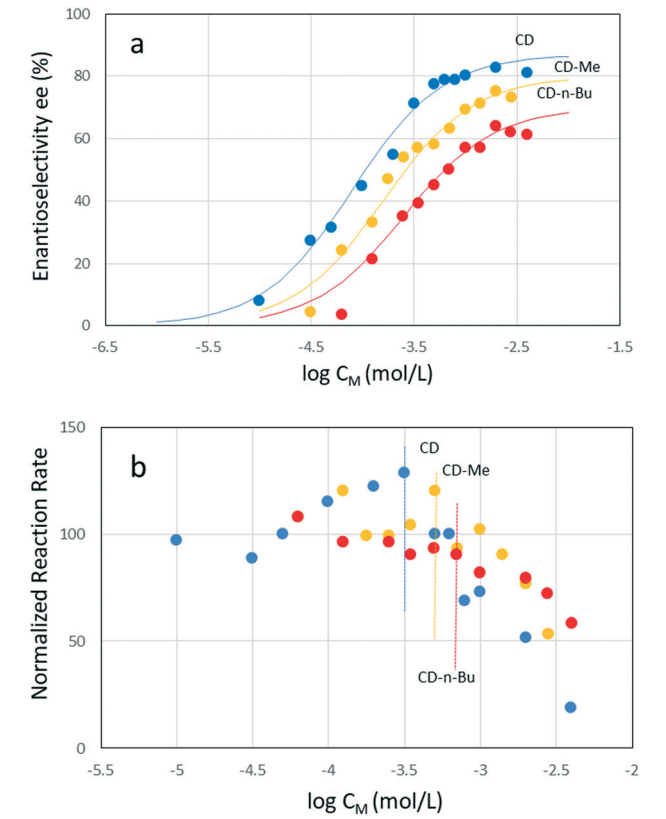


Fig. 1 a) Enantioselectivity, as expressed by ee%, as a function of the modifier concentration (C_M, mol L^{-1}) in a logarithm scale for the asymmetric hydrogenation of PCA over Pd/C modified with cinchona derivatives. Modifiers: CD (●), CD–Me (●), and CD–*n*-Bu (●). The smooth line for each modifier is the curve fitted by using the values of i^e (%) and $\log\beta$ in Table 2. b) Normalized initial reaction rate as a function of the modifier concentration (C_M, mol L^{-1}) in a logarithm scale. The vertical line indicates the concentration C_M^* (mol L^{-1}), at which a peak or hump is observed in the reaction rate for each modifier. The raw data for CD are taken from our previous study[49] and are shown for comparison.

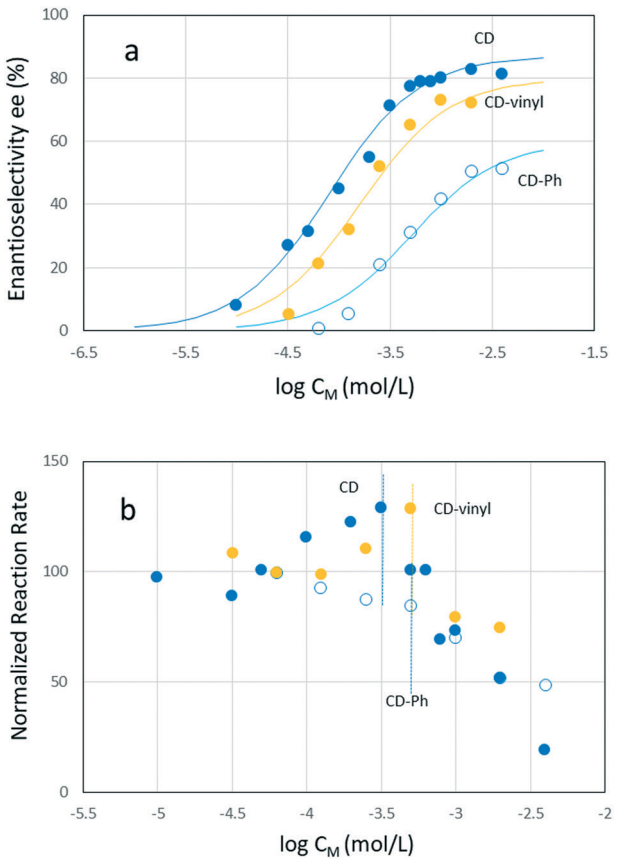


Fig. 2 a) Enantioselectivity, as expressed by ee%, as a function of the modifier concentration (C_M, mol L^{-1}) in a logarithm scale for the asymmetric hydrogenation of PCA over Pd/C modified with cinchona derivatives. Modifiers: CD (●), CD–vinyl (●), and CD–Ph (○). The smooth line for each modifier is the curve fitted by using the values of i^e (%) and $\log\beta$ in Table 2. b) Normalized initial reaction rate as a function of the modifier concentration (C_M, mol L^{-1}) in a logarithm scale. The vertical line indicates the concentration C_M^* (mol L^{-1}). The raw data for CD are taken from our previous study[49] and are shown for comparison.

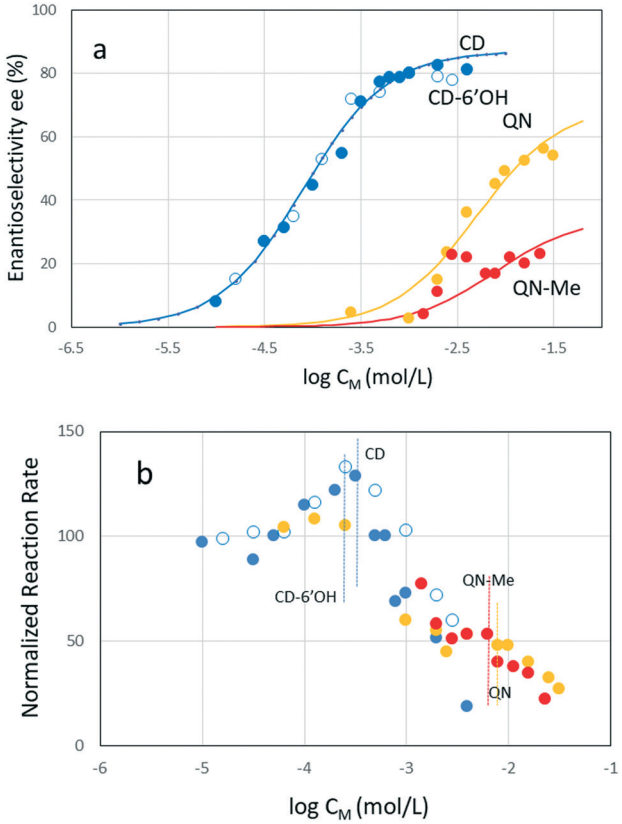


Fig. 3 a) Enantioselectivity, as expressed by ee%, as a function of the modifier concentration (C_M, mol L^{-1}) in a logarithm scale for the asymmetric hydrogenation of PCA over Pd/C modified with cinchona derivatives. Modifiers: CD (●), CD-6′OH (○), QN (●), and QN–Me (●). The smooth line for each modifier is the curve fitted by using the values of i^e (%) and logβ in Table 2. b) Normalized initial reaction rate as a function of the modifier concentration (C_M, mol L^{-1}) in a logarithm scale. The vertical line indicates the concentration C_M^* (mol L^{-1}). The raw data for CD, CD-6′OH and QN are taken from our previous study[49] and are shown for comparison.

Table 2 Kinetic analysis of the enantioselective hydrogenation of PCA over Pd/C modified with a cinchonidine derivative

Modifier	ee$^{max a}$ (%)	i^{eb} (%)	logβ^c	log $C_m^{*\,d}$	Δlogβ^e
CD	83	87	−4.1	−3.5	0
CD–Me	75	80	−3.8	−3.3	0.08
CD–vinyl	73	80	−3.8	−3.3	0.08
CD–*n*-Bu	64	70	−3.6	−3.2	0.19
CD–Ph	51	60	−3.3	−3.3sh	0.60
QN	56	70	−2.3	−2.1	0.36
QN–Me	23	35 ± 5	−2.1 ± 0.1	−2.2	0.64
CD-6′OH	80	85	−4.2	−3.6	0.0

[a] Maximum ee (%) observed for the modifier. [b] Intrinsic enantioselectivity i^e (%) defined by eqn (1) and (2). [c] Kinetic parameter $\beta = (k_u/k_m)(K_S/K_M)(1 + K_{MS}C_S)/K_{MS}$ in a logarithm scale. [d] Concentration of the modifier (C_M^*, mol L^{-1}) giving a reaction rate peak at the modified sites. [e] Logβ relative to that of cinchonidine after the correction for the K_M of the modifier.

asymmetric hydrogenation of ethyl pyruvate over a platinum catalyst modified with HCD.

As for the reaction rates of the PCA hydrogenation, an activity peak (ligand acceleration)[1,7,57–59] clearly observed with CD-modified Pd/C was decreased by the substitution and, in some cases, became ambiguous into a hump or shoulder peak. The reaction rates in Fig. 1b–3b are normalized by the reaction rate (140 mmol g^{-1} h^{-1}) observed in the absence of the modifier ($C_M = 0$) but in the presence of auxiliary additive BA (0.5 mmol). It is concluded that both the enantioselectivity and reaction rate of CD–Pd/C are decreased by the substitution at the 2′- and/or 6′-positions of the quinoline moiety of CD for the asymmetric hydrogenation of PCA. We analyzed the significant enantioselectivity changes observed in Fig. 1a–3a from the kinetic points of view to obtain information on the kinetic parameters controlling such changes.

The enantioselectivity of the asymmetric hydrogenation of PCA in Fig. 1a–3a was analyzed by the use of the kinetic modeling and formulations previously reported elsewhere.[57] We have assumed in the kinetic formulations that the modifier, substrate, hydrogen (dissociatively), and auxiliary additive BA are reversibly and competitively adsorbed on the palladium metal surface and that in the presence of BA (BA/PCA molar ratio = 1), the rate determining step of the reaction is the initial hydrogen atom addition to the adsorbed substrate at both modified and unmodified sites. The change of the rate determining step of the reaction from the desorption step of the products to a surface reaction was proposed by Nitta[27,60] and recently verified by Meemken *et al.*[25] using *in situ* ATR-IR. We have previously shown *syn*-addition of hydrogen to PCA over CD–Pd/C.[61] It is also assumed that enantioselective hydrogenation proceeds at the modified sites where a surface substrate–modifier 1:1 complex is formed.[20,27,30,38,47] Vargas and coworkers[16] have suggested by theoretical calculations with CD-modified platinum that the substrate likely approaches a chiral site either from solution or from a physisorbed state. In accordance with their suggestions, the formation of the complex intermediate has been formulated by the adsorption of the substrate onto the preadsorbed modifier, rendering the rate equations to be very simplified.[57] Under these assumptions and a Langmuir–Hinshelwood formalism, we have obtained eqn (1) to correlate the observed ee to the concentration of the modifier (C_M) in the reaction solution.[57] The detailed derivations of eqn (1) are presented in the ESI.†

$$\begin{aligned} ee &= i^e r_m/(r_m + r_u) \\ &= i^e/(1 + \beta/C_M) \end{aligned} \quad (1)$$

where $\beta = (k_u/k_m)(K_S/K_M)(1 + K_{MS}C_S)/K_{MS}$. r_m and k_m denote the reaction rate and rate constant at the modified sites, respectively, while r_u and k_u are those at the unmodified sites. K and C represent the equilibrium adsorption constant and concentration, respectively. The subscripts M, S and MS are the modifier, substrate and modifier–substrate complex, respectively. It is noted that K_{MS} is elucidated by the interactions between the substrate and surface modifier as

well as by the interactions of the substrate with surface palladium atoms. The intrinsic enantioselectivity i^e (%) in eqn (1) is defined by the ee of the hydrogenation at the modified sites.

$$i^e = 100 \times |[S]_m - [R]_m|/([S]_m + [R]_m) \quad (2)$$

where $[S]_m$ and $[R]_m$ represent the amounts of the *S* and *R* enantiomers formed *via* pro-*S* and pro-*R* intermediate complexes at the modified sites, respectively. eqn (1) is transformed into eqn (3).

$$\log[ee/(i^e - ee)] = \log C_M - \log \beta \quad (3)$$

eqn (3) predicts a linear correlation with a slope of unity between $\log[ee/(i^e - ee)]$ and $\log C_M$. The value of i^e cannot be directly determined by experiments in spite of its extreme importance in understanding the enantioselective hydrogenation mechanism. However, we can use eqn (3) to estimate it from the dependency of ee on the concentration of the modifier, C_M, by choosing the appropriate value of i^e so as to provide a theoretical linear correlation with a slope of unity over the widest C_M region.[57] In addition, we can obtain the value of $\log \beta$ from eqn (3). We applied eqn (3) to the analysis of the observed enantioselectivity in Fig. 1a–3a for the asymmetric hydrogenation of PCA over CD derivative-modified Pd/C to estimate the intrinsic enantioselectivity i^e and the kinetic parameter β in a logarithm scale.

Fig. 4 illustrates $\log ee/(i^e - ee)$ against $\log C_M$ for some representative modifiers after choosing the appropriate value of i^e. With the other modifiers used here, the best plots are shown in the ESI† (Fig. S1). Satisfactory linear correlations are obtained, validating the kinetic modeling and formulations used herein. The values of i^e and $\log \beta$ thus estimated are listed in Table 2. The simulation curves generated by the use of the values of i^e and $\log \beta$ in Table 2 are shown in Fig. 1a–3a and are compared with the observed ee for the modifiers. Satisfactory fittings are obtained, confirming the appropriateness of these values to describe the enantioselectivity as a function of $\log C_M$.

It is revealed in Table 2 that the intrinsic enantioselectivity of CD is decreased by the substitution at the 2′- and/or 6′-positions of the quinoline ring; i^e decreases in the order CD > CD–Me ~ CD–vinyl > CD–*n*-Bu > CD–Ph for the 2′-substitution and CD ~ CD-6′OH > QN ≫ QN–Me for the 6′- and 2′-substitutions. This order is roughly parallel to that of ee^{max}, although i^e is always larger than ee^{max} by definition. It is noted that the concentration to attain ee^{max} depends on the modifier. Both ee^{max} and the modifier concentration at ee^{max} for the asymmetric hydrogenation of the substrate are defined by kinetic factors such as the adsorption strength of the modifier relative to that of the substrate, reaction rate constant of the hydrogenation at the modified sites relative to that at unmodified racemic sites, interaction strength between the modifier and substrate and even the solubility of the modifier as well as the intrinsic enantioselectivity of the modifier–substrate interaction complexes. With the present series of the modifiers, the parallel correlation between ee^{max} and i^e leads us to conclude that the intrinsic enantioselectivity of the modifier is a dominant parameter to determine the observed maximum enantioselectivity.

The performance of the modifier in the asymmetric C═O and C═C hydrogenations on platinum and palladium, respectively, is sometimes evaluated at a fixed C_M. Fig. 1a–3a,

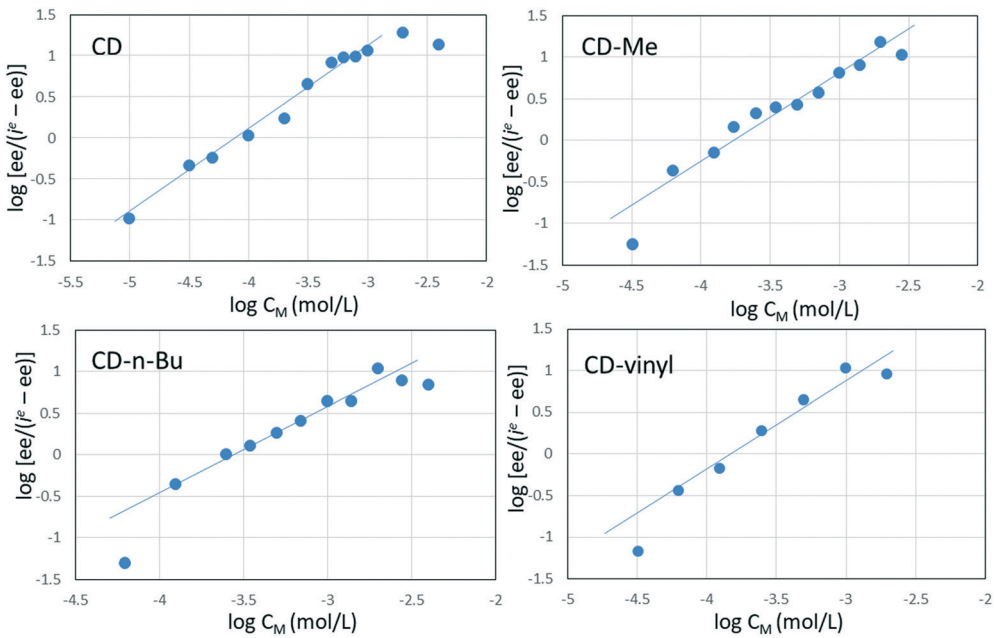


Fig. 4 Correlation between $\log[ee/(i^e - ee)]$ and $\log C_M$ for CD, CD–Me, CD–*n*-Bu, and CD–vinyl. The linear line in the plots is a hypothetical line with a slope of unity according to eqn (3). The values of i^e and $\log \beta$ thus obtained are listed in Table 2.

however, show that the modifier concentration to achieve ee^{max} considerably depends on the modifier. The enantioselectivity is determined by the kinetic parameters such as k_m/k_u, K_M/K_S, and K_{MS} as well as the intrinsic enantioselectivity, as presented by eqn (1). Thus, it is necessary to examine the enantioselectivity over as wide a concentration range of the modifier as possible for evaluating the performance of the modifier on the chirally modified novel metal catalysts.

The intrinsic enantioselectivity i^e of CD is significantly reduced by the substitution of the quinoline ring at the 2′- and/or 6′-positions, as presented in Table 2. It is presumed that the change in the i^e value is caused by the alteration in the adsorption geometry of the modifier by the substitution, which results in a conformational change in the chiral pocket formed by the adsorbed modifier on the palladium metal surface and thereby the change in the geometry of the modifier–substrate interaction complexes. From the kinetic points of view, these changes are reflected on the adsorption strength of the modifier and the interaction energy between the substrate and modifier. It is noted that these kinetic factors are included in the parameter β.

The relative adsorption strength of the modifier can be estimated from the modifier concentration, C_M^* (mol L^{-1}), at which the reaction rate shows a peak or hump (ligand acceleration).[57] By solving $dr_m/dC_M = 0$, eqn (4) can be derived (ESI†).

$$C_M^* = \alpha/K_M \quad (4)$$

where α is a constant so long as the same substrate is concerned. K_M is inversely proportional to C_M^*. From Fig. 1b–3b, the values of $\log C_M^*$ are elucidated and listed in Table 2. It is evident that the adsorption strength of the modifier, as expressed by K_M, is reduced by the substitution and decreases in the order: CD > CD–Me ~ CD–vinyl ~ CD–Ph ~ CD–*n*-Bu for the 2′-substitution and CD-6′OH ~ CD ≫ QN ~ QN–Me for the 6′- and 2′-substitutions. The decrease in the adsorption strength of CD by the methoxy-substitution at the 6′-position agrees with the observations by Huck *et al.*[39,40] The substitution of the quinoline ring of CD at the 2′-position by the methyl-, vinyl-, phenyl-, or *n*-butyl group induces a 1.6–2 times decrease of the K_M value $(\Delta \log C_M^* = 0.2\text{–}0.3)$. The methoxy-substitution at the 6′-position of CD to form QN shows much stronger effects, a 20–25 times decrease in K_M. On the other hand, the hydroxyl-group at the 6′-position exhibits no notable or even beneficial effects on the adsorption strength of CD (CD-6′OH). The substitution at the 2′-position of QN by a methyl-group does not cause any further decrease in the adsorption strength within the accuracy of $\log C_M^*$ (±0.1).

There is a vague tendency as shown in Table 2 that the intrinsic enantioselectivity decreases as the adsorption strength of the modifier decreases. It is generally accepted that CD is adsorbed on a geometry parallel to a platinum or palladium metal surface *via* π-electrons of the quinoline ring of CD in the energetically most stable adsorption mode.[1–10] It is considered that the weakening of the adsorption strength of CD by the substitution at the 2′-position of the quinoline moiety is caused by tilting of the quinoline ring around the short axis due to steric effects from the flat lying adsorption mode *via* π-electrons on the palladium metal surface. The methyl-, vinyl-, *n*-butyl- and phenyl-groups exhibit almost the same effects. Tilting of the quinoline ring around the long axis due to the methoxy-substitution at the 6′-position exhibits much stronger effects on the adsorption strength. Huck *et al.*[40] have shown from nonlinear effects observed with a modifier mixture of CD and QN or CN and QD over Pd/TiO_2 that QN/QD is adsorbed more weakly than CD/CN due to the tilting of the quinoline ring relative to the palladium metal surface by the introduction of the methoxy-group at the 6′-position. It is proposed herein that the tilting of the quinoline ring of the CD-derivative modifier around its short and/or long axes results in the change in the conformation of the chiral pocket constituted by the adsorbed modifier and, thereby, in the alteration of the intrinsic enantioselectivity. Kubota and Zaera[62] have demonstrated by *in situ* RA-IR that the flat-lying geometry of the modifier is responsible for the enantioselective hydrogenation of ethyl pyruvate over an HCD-modified platinum catalyst. Thus, as far as a series of the CD-derivatives is concerned, the adsorption strength of the modifier may be related to the intrinsic enantioselectivity, though qualitatively and indirectly.

To seek the other kinetic factors more directly correlated to the intrinsic enantioselectivity, we tried to separate the effects of the adsorption strength of the modifier from the parameter β. Taking into consideration the weak dependency of ee on the substrate concentration, C_S,[57] we can estimate more relevant parameters, as follows.

$$\begin{aligned}\log\beta &= \log(k_uK_S) - \log K_M - \log k_m + \log[(1 + K_{MS}C_S)/K_{MS}] \\ &\sim \log(k_uK_S) - \log K_M - \log(k_mK_{MS}) \quad (5)\end{aligned}$$

Combining eqn (5) with eqn (4),

$$\log\beta \sim \log(k_uK_S/\alpha) - \log(k_mK_{MS}) + \log C_M^* \quad (6)$$

Since the term k_uK_S/α is common for the same substrate concerned, eqn (6) predicts a linear correlation with a slope of unity between $\log\beta$ and $\log C_M^*$ for the substrates exhibiting the same k_mK_{MS}. Fig. 5 presents $\log\beta$ against $\log C_M^*$ together with a hypothetical linear line having a slope of unity, expected for a modifier having the same k_mK_{MS} as that of CD but with varying K_M. The difference in $\log\beta$ for each modifier, $\Delta\log\beta$, from the linear line at its value of $\log C_M^*$ shows the difference in $\log(k_mK_{MS})$ from that of CD. Thus, Fig. 5 can be used to estimate $\log(k_mK_{MS})$ of a modifier, relative to that of CD, from $\log\beta$ after the correction of the effect of the adsorption strength of the modifier. The values of $\Delta\log\beta$ thus obtained from Fig. 5 are summarized in Table 2.

Fig. 6 shows a correlation between the intrinsic enantioselectivity and $\Delta\log\beta$. The intrinsic enantioselectivity

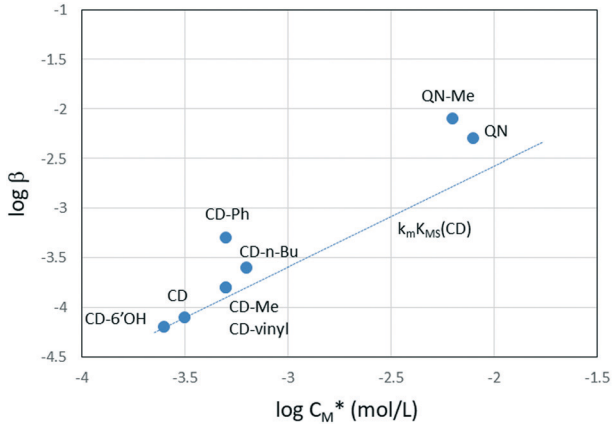


Fig. 5 $\log\beta$ against $\log C_M^*$ (mol L^{-1}) for the asymmetric hydrogenation of PCA over CD derivative-modified Pd/C. The dotted line through the points for CD is a hypothetical line with a slope of unity, expected for a modifier exhibiting the same k_mK_{MS} value as that of CD but with varying K_M, according to eqn (6).

i^e decreases as $\Delta\log\beta$ increases or k_mK_{MS} decreases regardless of the substitutions at the 2′- and 6′-positions. A satisfactory and simple relationship in Fig. 6 implies that i^e is defined by k_mK_{MS} from the kinetic points of view. Unfortunately, k_m and K_{MS} are not decoupled in the present study. In our previous study on the enantioselective hydrogenation of ketones over a tartaric acid-modified RANEY®-type Ni catalyst, we suggested by combining kinetic analysis and DFT calculations that the enantioselectivity increased as the interaction energy between the modifier–substrate or K_{MS} in the present description increased.[63] Theoretical calculations by Schmidt *et al.*[20] have shown with the enantioselective hydrogenation of trifluoroacetophenone over CD- and CN-modified platinum catalysts that the interaction energy difference, ΔE, between the pro-*S* and pro-*R* substrate–modifier surface complexes is a controlling factor over the (intrinsic) enantioselectivity (thermodynamic control). It is conceivable that the energy difference between the pro-*S* and pro-*R* modifier–substrate interaction complexes increases as the magnitude of K_{MS} increases for a series of interaction complexes possessing a similar structure. Actually, according to the calculations by Schmidt *et al.*,[20] ΔE for CD (2.2 kcal mol^{-1}) is larger than that for CN (1.0 kcal mol^{-1}) and the magnitude of interaction energy averaged over the pro-*R* and pro-*S* complexes for CD (30.0 kcal) is larger than that for CN (28.9 kcal mol^{-1}). The simple correlation in Fig. 6 prompts us to speculate that stronger interactions between the substrate and surface modifier result in a larger energy difference between the pro-*R* and pro-*S* intermediate surface complexes and, thereby, are beneficial for achieving a higher intrinsic selectivity in the asymmetric hydrogenation of PCA over the present series of CD derivative-modified Pd/C. As discussed above, it is considered that the substitutions at the 2′- and 6′-positions of the quinoline ring of CD result in the tilting of the modifier molecule around the short and long axes of the ring, respectively, relative to the palladium metal surface, accompanying the decrease in the adsorption energy (as expressed by K_M). It is argued that the modification of the adsorption geometry of cinchona molecules alters the conformation of the chiral pocket formed by the stereogenic quinuclidine moiety and C9–OH on the linker, and thereby the intrinsic enantioselectivity. Schmidt *et al.*[20] have, on the other hand, pointed out from the theoretical calculations on the asymmetric hydrogenation on 9-*epi*-CD-modified platinum that the concept of the thermodynamic control is not generally applicable to predict the stereochemical outcomes. It is actually considered that k_m and K_{MS} are in some cases strongly coupled with each other[7] (for instance, compensation effects[64,65]); an increase of K_{MS} may accompany a decrease of k_m due to enhanced activation energy and *vice versa*.

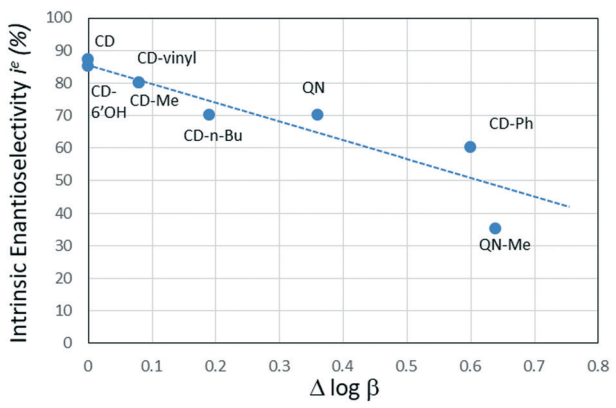


Fig. 6 Correlation between the intrinsic enantioselectivity i^e (%) and $\Delta\log\beta$.

Rodríguez-García *et al.*[26] have demonstrated with CN–Pd/TiO_2 by *in situ* ATR-IR combined with UV-vis that the adsorption geometry of CN depends strongly on the surface coverage of the modifier. Combining the ATR-IR results with the selectivity and activity of the hydrogenation of 4-methoxy-6-methyl-2-pyrone on CN–Pd/TiO_2, they suggested that less stable CN species with a tilted aromatic ring anchor provided a stronger enantioselective control. Meemken *et al.*[25] have shown by a time resolved ATR-IR spectroscopic study that two types of adsorbed CD are detected on Pd/TiO_2, π-bonded CD and N-lone pair bonded CD, in the absence of BA, but that the coexistence of CD and BA leads to a dynamic transformation of N-lone pair bonded CD to π-bonded CD. In consequence, we are inclined to tentatively suggest from the present kinetic study that in the presence of BA, a (almost) flat-lying adsorption geometry of CD on the palladium metal surface is beneficial for achieving a high enantioselectivity and that the introduction of the substituent(s) at the quinoline ring alters the geometry to a tilted one due to steric hindrance, accompanying decreases in the adsorption strength of the modifier, the substrate–modifier interaction energy, and thereby the intrinsic enantioselectivity. Further studies on the microkinetics coupled with molecular modeling and theoretical calculations are needed for better understanding of the controlling parameters of the intrinsic

enantioselectivity in the asymmetric hydrogenations on chirally modified palladium and platinum metal catalysts.

Experimental

Reaction procedures

All chemicals were purchased from commercial sources and purified *via* distillation when necessary. The enantioselective hydrogenation reaction of (*E*)-2,3-diphenylpropenoic acid (α-phenylcinnamic acid, PCA) was carried out over chiral cinchonidine derivative-modified Pd/C.[30,49,57,58] In brief, a stirred suspension of 5% Pd/C (43 mg as a 50% content, wet form STD-type supplied by N.E. Chemcat) and 5 mL of 2.5% H_2O-containing dioxane (wet dioxane) as a solvent was heated under 0.1 MPa of hydrogen at 353 K for 30 min. After cooling to 296 K, a solution of the modifier (5.1×10^{-6} – 41×10^{-3} mmol) in the solvent (1 mL) was added. After 30 min, 0.5 mmol PCA in the solvent (4 mL) and then benzylamine (BA, 0.5 mmol) was added, while vigorously stirring (1200 rpm). The reaction temperature and pressure were 296 K and 0.1 MPa of hydrogen, respectively. The initial reaction rate was calculated from the rate of hydrogen consumption at 25% conversion. The hydrogen consumption continued for 1–3 h before completion. After additional 2 h, 2 M HCl aq. (1 mL) was added to the solution and the mixture was filtered to remove the catalyst. The filtrate was extracted with ethyl acetate (2 mL) and washed with water (2 mL). The extract was analyzed by HPLC with a chiral column (Daicel OJ-3). The enantioselectivity is expressed as the enantiomeric excess (ee) of the *S* or *R* enantiomer,

$$\mathrm{ee} = 100 \times |[S] - [R]|/([S] + [R]),$$

where $[S]$ and $[R]$ represent the concentrations of the *S* and *R* enantiomers, respectively. The experimental reproducibility of ee was usually ±2% under the present reaction conditions.

Synthesis of cinchonidine derivatives

According to the reported procedures,[66–68] the substitution of the quinoline ring of cinchonidine (CD) was carried out by the use of alkyl- or phenyl-Li to yield 2′-substituted derivatives, CD–Me, CD–*n*-butyl or CD–Ph. In brief, for instance, CD was treated with MeLi (3 eq.) at 195 K in THF under N_2 atmosphere. The solution turned yellow in color after 12 h. Then, the reaction was quenched by adding an aqueous solution of $NaHCO_3$, followed by extraction of the product with ethyl ether. After confirming the complete loss of 2′-H of CD by NMR, the product was treated with I_2 in THF for 2 h. The reaction mixture was extracted with ethyl ether in the presence of a Na_2SO_3 aqueous solution, followed by purification with SiO_2 column chromatography (eluent: $MeOH/CHCl_3$) and with recrystallization from ethyl acetate to yield CD–Me in 14% yield as a white solid. The formations of CD–Me, CD–*n*-Bu, and CD–Ph were confirmed by ^{1}H- and ^{13}C-NMR, IR and MS techniques.[66–68] The NMR data of these compounds agreed very well with those reported in literature.[66–68] The yields of CD–*n*-Bu and CD–Ph were 28% and 35%, respectively. QN–Me was synthesized and characterized similarly (yield, 18%).[66,67] CD–vinyl was synthesized by a reaction of CD with vinyl-MgBr and characterized by NMR and MS (yield, 14%) according to the synthesis procedures and characterization techniques by Yardley *et al.*[66] The chemical data for CD–vinyl are presented in the ESI.† CD-6′OH was prepared by demethylation of QN and characterized accordingly (yield, 65%).[49,69]

Conclusions

Asymmetric hydrogenations of α,β-unsaturated carboxylic acids over cinchona alkaloid-modified palladium metal heterogeneous catalysts have received considerable attention because of their scientific importance in molecular recognition catalysis and feasibility of industrial applications. In the present study, the effect of the quinoline ring modification of cinchonidine (CD) on the enantioselective hydrogenation of α-phenylcinnamic acid (PCA) was systematically analyzed from the kinetic points of view. The substitution at the 2′- and/or 6′-positions of the quinoline moiety by methyl, vinyl, *n*-butyl or phenyl decreased the observed enantioselectivity over the whole range of the modifier concentration. The present kinetic analysis of the enantioselectivity allowed us to estimate the intrinsic enantioselectivity at the modified sites and the adsorption strength of the modifier. It is revealed that the substitution at the quinoline ring of CD reduces the adsorption strength of the modifier, probably due to the tilting of the quinoline ring from a flat-lying adsorption geometry, accompanying a decrease in the intrinsic enantioselectivity of CD. The intrinsic enantioselectivity is correlated to a kinetic parameter, most likely, to the modifier–substrate interaction energy. It is proposed that the tilting of the quinoline ring of the CD-derivative modifier around its short and/or long axes results in the change in the conformation of the chiral pocket constituted by the adsorbed modifier and, thereby, in the alteration of the intrinsic enantioselectivity. It is suggested that the present kinetic model and formulation can be generally applied to describe the catalytic behaviors and performance of cinchona-modified palladium and platinum catalysts for the asymmetric hydrogenations because of their identical reaction schemes from the kinetic viewpoints: reversible adsorption of the substrate and modifier, formation of a surface substrate–modifier interaction complex, and subsequent hydrogen addition, followed by desorption of products.

Conflicts of interest

There are no conflicts to declare.

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