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Enantio-differentiating hydrogenation of alkyl 3-oxobutanoates over tartaric acid-modified Ni catalyst: Enthalpy-entropy compensation effect as a tool for elucidating mechanistic features



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ABSTRACT

The enantio-differentiating hydrogenations of a series of alkyl 3-oxobutanoates were carried out at the temperatures ranging from 333 to 393 K over the (R,R)-tartaric acid-modified Ni catalyst prepared from commercially available Ni powder to achieve high enantiomeric excesses of 91-94%. It was demonstrated that the enantio-selectivity was not a simple function of the reaction temperature, being enhanced in the low temperature region to reach a maximum at 363–373 K and then decreased at higher temperatures. Nevertheless, all the differential enthalpies and entropies of activation calculated from the enantio-differentiation mechanism over the entire temperature range. A plausible enantio-differentiation mechanism explaining the effects of hydrogenation temperature on the enantio-selectivity is proposed.

1. Introduction

The production of optically active compounds is a key issue in synthetic organic chemistry, especially for the synthesis of pharmaceuticals, flavor and aroma chemicals, and agrochemicals. A variety of chiral catalysts, both homogeneous (organometallic complexes, enzymes, and organocatalysts) [1–5] and heterogeneous (modified solid catalysts, heterogenized organometallic complexes, enzymes, and metal-organic frameworks) [6–17], have hitherto been employed for this purpose. Among them, chirally modified solid catalysts are particularly promising and advantageous for the large-scale production in industry. This is because they are readily prepared at low cost, separable from the reaction mixture, and reusable without any additional treatments, all of which are attractive also from the ecological and economical viewpoints [18].

Tartaric acid (TA)-modified Ni catalyst is one of the most successful chiral solid catalysts for the enantio-differentiating hydrogenation of β -keto-esters (KEs) [19–21] and 2-alkanones [22–24]. This catalyst is usually prepared by adsorbing TA and NaBr on surface-activated Ni catalyst, such as Raney Ni [25–27]. However, there is a serious drawback of this catalyst that the chiral modification has to be carried out

immediately after the preparation of Raney Ni from Al-Ni alloy; otherwise the nickel catalyst undergoes fast surface oxidation leading to poor reproducibility [28]. Recently, we found that the TA-modified Ni catalyst prepared from commercial Ni powder without any pretreatment also functions as an equally effective and highly robust catalyst for the enantio-differentiating hydrogenation of KEs to give the corresponding hydroxyesters (HEs) with the enantio-selectivities higher than those obtained with conventional TA-modified Raney Ni [29]. The catalyst can be prepared simply by soaking Ni powder in an aqueous solution of TA and NaBr without potentially hazardous pre-activation by hydrogen gas, and is therefore more suitable for industrial use from the safety aspect.

In this study, to optimize the reaction conditions for better enantioselectivity and also to elucidate the factors and mechanism controlling the enantio-differentiating hydrogenation, we expanded the range of substrates (Scheme 1) and closely examined the effects of hydrogenation temperature on the enantio-selectivity to reveal that the enantiomeric excess (*e.e.*) is not a simple function of the temperature to reach a maximum in the middle of the temperature range examined. The enantiomer ratio (*e.r.*) obtained at each temperature was subjected to the Eyring analysis to afford the differential activation parameters,

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Scheme 1. Enantio-differentiating hydrogenation of alkyl 3-oxobutanoates to hydroxyesters over nickel powder modified with (R,R)-tartaric acid and NaBr.

from which the origin of unconventional temperature-dependence of the *e.e.* value is elucidated.

2. Experimental Section

2.1. Materials

Methyl acetoacetate (> 95%), ethyl 3-oxobutanoate (> 98%), acetic acid (> 99.7%), tetrahydrofuran (> 99.5%), tartaric acid (> 99.5%), and sodium bromide (> 99.5%) were purchased from Wako Pure Chemical Industries, Ltd. Propyl 3-oxobutanoate (> 98%), butyl 3-oxobutanoate (> 98%), isopropyl 3-oxobutanoate (> 97%), and 2-methylpropyl 3-oxobutanoate (> 98%) were purchased from Tokyo Chemical Industry Co., Ltd. All the chemicals were used as received. Ni powder of 5 µm diameter was purchased from Sigma-Aldrich Japan K.K.

2.2. Enantio-differentiating hydrogenation of alkyl 3-oxobutanoates (1a-1f)

Commercially available nickel powder was directly subjected to the chiral modification without any pre-activation by hydrogen gas, according to the procedures described previously [30]. Briefly, nickel powder (0.5 g) was immersed for 1 h in an aqueous solution (50 cm³) containing (R,R)-TA (0.5 g) and NaBr (2.0 g) at 373 K, the pH of which was adjusted to 3.2 by using a $1 \mod dm^{-3}$ NaOH solution before modification. After the modification, the Ni catalyst was successively washed once with deionized water (10 cm³), twice with methanol (25 cm³ each), and then twice with THF (10 cm³ each). The modified catalyst was added to a mixture of alkyl 3-oxoalkanoate (21.5 mmol), acetic acid (0.1 g), and THF (10 cm³) placed in an autoclave equipped with a magnetic stirrer (OM Lab-Tech Co., Ltd., Tochigi, Japan). The autoclave was pressurized to 9 MPa with hydrogen gas and heated to a desired temperature. The mixture was stirred for 20 h at a constant rate of 1370 rpm. Then, the pressure was released and the catalyst was removed from the reaction mixture by decantation with the aid of magnet. The conversion was determined by GLC analysis using a Hitachi 263-30 instrument equipped with a 5% Thermon 1000-coated Chromosorb W column (3 mm I.D. \times 2 m).

2.3. Determination of enantio-selectivity

The hydrogenated products were derived to the corresponding acetyl esters by treating with acetyl chloride and their *e.e.* values were determined by chiral GLC using a Shimadzu GC-18A instrument equipped with a CP Chirasil DEX-CB column (0.25 mm x 25 m) [31]. The retention times of the enantiomers of each product are listed in Table S1 in the Supporting Information. The e.e. value was calculated

from the integrated areas of the enantiomer peaks. Repeated experiments gave nearly the same *e.e.* values with high reproducibility; the error of *e.e.* $\leq 1\%$.

3. Results and discussion

3.1. Enantio-differentiating hydrogenation of alkyl 3-oxobutanoates (1a-1f)

The enantio-differentiating hydrogenations of 1a-1f were carried out at 333 – 393 K. The conversions and the product's *e.e.* obtained with the TA-modified Ni powder as well as the *e.e.* values reported for the modified Raney Ni are summarized in Table 1.

The conversions were (quasi-)quantitative at temperatures \geq 373 K for all the substrates examined, but started to decrease at 363 K and substantially diminished down to 3-8% at 333 K. No straightforward relationship was found between the conversion and the alkyl (R') size even at the lowest temperature examined. In contrast, the highest enantio-selectivities were consistently attained in the middle of temperature range employed, i.e. 363 to 373 K, without any exception. This enabled us to achieve the highest enantio-selectivity with a nearly quantitative conversion. The highest *e.e.* values obtained for **1a-1f** at 363–373 K are consistent with the previous data reported by us [34]. It was shown that the enantio-selectivity was slightly smaller for the methyl ester (**1a**) than for the longer/bulkier groups (**1b-1f**), although the difference was only 1-3%.

Earlier, the enantio-differentiating hydrogenations of various alkyl 3-oxobutanoates with the TA-modified Raney Ni catalyst prepared similarly have been investigated by Tai et al. [31,32]; the reported *e.e.* values are also listed in Table 1 for a comparison purpose. The highest enantio-selectivities obtained by using TA-modified Ni powder in the present study are consistently higher than those attained with TA-modified Raney Ni under comparable conditions. Another major difference was found in the temperature dependence of e.e. In the Raney Ni case, the enantio-selectivity does not appreciably depend on the hydrogenation temperature, whereas the e.e. value rapidly decreases with lowering the temperature particularly below 363 K in the Ni powder case.

Before discussing the activation parameters calculated from the *e.e.* data obtained, we scrutinized the conceivable influences of reaction parameters such as conversion, hydrogen pressure, and the desorption of modifiers, as well as the potential racemization of hydrogenated products.

The effect of conversion on *e.e.* in heterogeneous hydrogenation over TA-modified nickels has been examined by several groups [35–37]. One of the factors leading to conversion-dependent *e.e.* is the difference in induction period of the enantio-differentiating (e.d.) versus non-enantio-differentiating (non-e.d.) site; thus, the lowered e.e.

Table 1

Enantio-differentiating hydrogenation of alkyl 3-oxobutanoates (CH₃COCH₂CO₂R) over TA-modified Ni powder and Raney Ni.

Substrate (R')	Hydrogenation	Ni powder		Raney Ni ^a
	temperature/ k	Conversion/%	e.e./%	0.0.7 /0
1a (Me)	393	100	81	
	383	100	89	
	373	100	89	86
	363	98	90	
	353	71	87	
	343	29	85	
	333	8	61	86
1b (Et)	393	100	88	
	383	96	92	
	373	97	94	88
	363	90	92	
	353	42	90	
	343	23	84	
	333	4	61	
1c (Pr)	393	100	88	
	383	100	91	
	373	100	92	88
	363	74	92	
	353	39	91	
	343	21	89	
	333	3	38	
1d (Bu)	393	100	88	
	383	100	91	
	373	87	93	88
	363	74	92	
	353	43	91	
	343	22	88	
	333	4	39	
1e (iPr)	393	98	86	
	383	100	91	
	373	98	92	85
	363	90	94	
	353	58	92	
	343	21	83	
	333	6	54	87
1f (iBu)	393	100	88	
	383	100	92	
	373	97	94	
	363	77	92	
	353	49	90	
	343	31	86	
	333	7	46	

^a Data from references [31], [32] and [33], where only the *e.e.* values are reported at one or two temperatures without mentioning to the conversion.

observed in the early stage of reaction is explained by the longer induction period of the e.d. site) [35]. Keane reported that the enantioselectivity is slightly reduced to 29% *e.e.* at a very low conversion (5%) but recover to a constant value (31% *e.e.*) at conversions $\geq 20\%$ [36]. More recently, Kukula and Cervený have shown that the induction period becomes longer when the rate of reaction is slower [37].

In the present study, the effect of conversion on *e.e.* was negligible within the experimental error ($\pm 1\%$) upon hydrogenation of **1a** and **1b** at 373 K, affording constant 87-88% and 91-92% *e.e.*, respectively, over a wide range of conversion, i.e. 20-100%, although the e.e. for **1a** was appreciably decreased to 84% at 14% conversion, as shown in Table S2. For this reason, all the e.e. data obtained at 333 K, where the conversions were well below 10%, were not taken into consideration in the Eyring analyses in the following section.

Racemization of the hydrogenated product was examined by treating methyl 3-hydroxybutyrate of 83.6% *e.e.* at 393 K for 20 h under exactly the same reaction conditions employed for the hydrogenation over TA-modified Ni powder to recover the hydroxy-ester in essentially the same 82.7% *e.e.*

The effects of the desorption of modifiers during the reaction on *e.e.* would also be negligible. Even when the small amounts of the modifiers

were desorbed from the nickel surface, no deterioration of the *e.e.* was observed at least upon repeated use of TA-modified Ni catalyst prepared from nickel oxide; for detailed analysis data for the amount of adsorption species and *e.e.*, see Table S3 in the Supporting Information.

The effect of hydrogen pressure has already been examined for the hydrogenation of methyl acetoacetate (1a) over TA-NaBr-modified Ni powder to reveal that the product *e.e.* is not affected by hydrogen pressure to afford constant 90-91% at least in the pressure range of 9–11 MPa [29]. This result also indicates that the concentration of hydrogen gas in the liquid phase does not affect the *e.e.* under the present reaction conditions.

3.2. Differential activation parameters for enantio-differentiation: Enthalpy-entropy compensation

To obtain a global picture of the enantio-differentiating hydrogenation as well as insights into the origin and mechanism of the unprecedented irregular temperature-dependence of product's *e.e.* in the catalytic hydrogenation of **1a-1f** over TA-modified Ni powder, we employed the Eyring approach [38] to this heterogeneous catalytic hydrogenation system.

As widely accepted in the literature [6,39–42], the enantio-differentiating hydrogenation of KE over TA-modified Ni catalyst (Ni-TA) proceeds through a pair of diastereomeric transition states [Ni-TA-*re*-KE][‡] and [Ni-TA-*si*-KE][‡] (where *re*-KE and *si*-KE denote the enantiotopically differentiated substrate upon interaction with TA on the Ni surface), which eventually afford an enantiomer pair of hydroxyesters, (*R*)-HE and (*S*)-HE, upon subsequent hydrogenation. Fig. 1 illustrates the energy profile for the catalytic hydrogenation of **1a-1f** where (*R*)product is favored.

In the energy profile shown in Fig. 1, the net free energy of activation for the formation of (*R*)- or (*S*)-HE, i.e. $\Delta G^{\ddagger re}$ or $\Delta G^{\ddagger si}$, is expressed by a sum of the apparent free energy for the adsorption of KE to TA on the Ni surface with the enantiotopic *re* or *si* face exposed to the bulk solution (ΔG_{ad}^{re} or $\Delta G_{ad}^{\ddagger si}$) and that for the addition of hydrogen atom to the adsorbed KE ($\Delta G_{H}^{\ddagger re}$ or $\Delta G_{H}^{\ddagger si}$) as follows.

$$\Delta G^{\ddagger re} = \Delta G_{\rm H}^{\ddagger re} + \Delta G_{\rm ad}^{r}$$

/

 $\Delta G^{\ddagger si} = \Delta G_{\rm H}^{\ddagger si} + \Delta G_{\rm ad}{}^{si}$

Experimentally, we can evaluate the apparent differential free energy of activation $(\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger r} - \Delta G^{\ddagger si})$ from the enantiomer ratio, *e.r.* = (*R*)-HE/(*S*)-HE, using Eq. (1).



Fig. 1. A schematic illustration of the energy profile for the enantio-differentiating hydrogenation of keto-ester (KE) to (*R*)- and (*S*)-hydroxyester (HE) over (*R*,*R*)-TA-modified Ni catalyst via a pair of diastereomeric transition states $[Ni-TA-re-KE]^{\ddagger}$ and $[Ni-TA-si-KE]^{\ddagger}$.



Fig. 2. Differential Eyring plots of the enantiomer ratios obtained in the enantio-differentiating hydrogenation of **1a** (R = Me) over TA-modified Ni powder in the high and low temperature regions (green triangles and blue circles, respectively); the *e.e.* data at 333 K (crossed out in the graph) is less reliable due to the very low conversion and hence not taken into consideration in the subsequent quantitative treatments.

$$\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger re} - \Delta G^{\ddagger si} = -RT\ln(e, r.)$$
⁽¹⁾

where *R* represents the gas constant. By combining the Eq. (1) with the differential form of Gibbs-Helmholtz equation $(\Delta\Delta G^* = \Delta\Delta H^* - T\Delta\Delta S^*)$, we obtain Eq. (2).

$$\ln(e. r.) = -\frac{\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} = -\frac{\Delta H^{\ddagger re} - \Delta H^{\ddagger si}}{RT} + \frac{\Delta S^{\ddagger re} - \Delta S^{\ddagger si}}{R}$$
(2)

This equation allows us to evaluate the differential activation enthalpy $(\Delta\Delta H^{\dagger})$ and entropy $(\Delta\Delta S^{\dagger})$ for the enantio-differentiating hydrogenation over TA-modified Ni powder. Indeed, the plot of $\ln(e.r.)$ calculated from the *e.e.* values (Table 1) as a function of the inverse temperature gave a good straight line in each of the low and high temperature regions, as exemplified for **1a** in Fig. 2; for the plots for other substrates, see Fig. S1 in the Supporting Information.

An apparently resembling bent Eyring plot has been reported for the diastereo-differentiating Paternó-Büchi reaction of cyclohexanoates with ketone [43], the origin of which was shown to be the switching of diastereo-differentiation step by temperature.

From the slope and intercept of the regression line, the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values were obtained for each region, as listed in Table 2.

Over the entire range of temperature examined, (*R*,*R*)-TA-modified Ni catalyst consistently affords (*R*)-HE in good-to-high enantio-selectivities (Table 1). However, its origin turned out to be totally different in the low and high temperature regions. The activation parameters obtained (Table 2) revealed that the high enantio-selectivity is exclusively driven by the positive differential entropy of activation ($\Delta\Delta S^{\ddagger} > 0$) in the low temperature region, but by the negative differential enthalpy of activation ($\Delta\Delta H^{\ddagger} < 0$) in the high temperature region. One of the plausible explanations for this alteration in the driving force, as well as for the obviously bent plot (Fig. 2), would be switching

Table 2

Differential activation parameters for the enantio-differentiating hydrogenation of alkyl 3-oxolkanoates 1-4 with TA-modified Ni powder in the temperature ranges 343–363 K and 373–393 K.^a

Substrate	343–363 K		373–393 K		
	$\Delta\Delta H^{\ddagger}/kJ$ mol ⁻¹	$\Delta\Delta S^*/J$ mol ⁻¹ K ⁻¹	$\Delta\Delta H^{*}/kJ$ mol ⁻¹	$\Delta\Delta S^{\ddagger}/J$ mol ⁻¹ K ⁻¹	
1a	23	89	-35	-70	
1b	38	132	-22	-32	
1c	21	84	-25	-41	
1d	22	86	-30	-54	
1e	51	169	-29	-52	
1f	31	112	-38	-74	

^a $\Delta\Delta H^{\ddagger} = \Delta H_{R}^{\ddagger} - \Delta H_{S}^{\ddagger}$; $\Delta\Delta S^{\ddagger} = \Delta S_{R}^{\ddagger} - \Delta S_{S}^{\ddagger}$, The $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values were obtained by the analysis of the *e.e.* values at different temperatures (Table 1) using Eq. (2).



Fig. 3. Enthalpy-entropy compensation plot of the differential activation parameters obtained in the enantio-differentiating hydrogenation of various alkyl 3-oxoalkanoates over TA-modified Ni powder catalyst (open and closed blue circles for the high and low temperature regions) and Raney Ni catalyst [20] (yellow diamonds).

of the effective enantio-differentiation step involved. In this catalytic reaction, the hydrogen addition is slowed down at lower temperatures to dominate the overall rate of hydrogenation. While the amount of KE on the TA-modified Ni surface decreases, the hydrogen addition to KE from both the enantiotopic *re-* and *si*-faces becomes faster to approach the diffusion limit of hydrogen (where no enantio-differentiation is expected to occur) at higher temperatures and the overall hydrogenation is governed by the desorption thermodynamics. Combining these considerations with the activation parameters obtained experimentally, we may assume that the hydrogen addition to adsorbed KE is entropically controlled, while the adsorption/desorption process is enthalpically driven. However, gaining further evidence for this hypothesis does not appear to be feasible due to the lack of tools to evaluate separately the rates and equilibria of heterogeneous catalysis. More detailed discussion of this topic is presented in Section 3.3.

Of particular interest, all of the $\Delta \Delta H^{\ddagger}$ and $\Delta \Delta S^{\ddagger}$ values obtained in both the low and high temperature regions (Table 2) perfectly compensate with each other to give a single straight line shown in Fig. 3 (blue circles), despite the temperature switching of enantio-differentiating step (vide supra) [44]. Furthermore, the activation parameters calculated from the data reported for the catalytic hydrogenation of a series of alkyl 3-oxoalkanoates (R = Me, Et, Pr, Bu, hexyl, cPr, cyclopentyl, cyclohexyl, neopentyl, R' = Me and R = Pr, R' = Me) over TAmodified Raney Ni [20] are plotted very closely to the same line (Fig. 3, vellow circles). The regression analysis of all the plotted data affords an empirical equation: $\Delta \Delta H^{\ddagger} = 365 \Delta \Delta S^{\ddagger} - 9.89$ (correlation coefficient r = 0.9979). The slope of regression line has a dimension of temperature and is called isokinetic temperature [45], which is 365 K in the present system. By incorporating the above empirical equation into the differential Gibbs-Helmholtz equation, $\Delta\Delta G^{\dagger} = \Delta\Delta H^{\dagger} - T\Delta\Delta S^{\dagger}$, we obtained the following equations:

$$\Delta \Delta G^{\text{\tiny Ξ}} = (365 - T) \ \Delta \Delta S^{\text{\tiny Ξ}} - 9.89$$

 $\Delta \Delta G^{\ddagger} = (1 - T/365) \Delta \Delta H^{\ddagger} - 9.89(T/365)$

where $\Delta\Delta G^{\ddagger}$ is expressed solely by $\Delta\Delta S^{\ddagger}$ or $\Delta\Delta H^{\ddagger}$. These equations indicate that the enantio-selectivity becomes identical at 365 K for all the substrates to afford the same *e.e.* of 96% (corresponding to the $\Delta\Delta G^{\ddagger}$ value of $-9.89 \text{ kJ mol}^{-1}$), irrespective of the R/R' substituents and the Ni catalyst (Ni powder or Raney Ni).

Similar compensatory enthalpy-entropy relationship has been

Ni-TA + KE [Ni-TA...*r*e-KE]
$$\xrightarrow{k_{\rm H}^{re}}$$
 [Ni-TA...*(R)*-HE] $\xrightarrow{k_{\rm d}^{re}}$ Ni-TA + (*R*)-HE
Ni-H [Ni-H] $\xrightarrow{k_{\rm d}^{si}}$ Ni-TA + (*R*)-HE

observed for the activation parameters derived from the enantiomeric ratios obtained in the photosensitized enantio-differentiating geometrical isomerization of (Z)-cyclooctene to chiral (E)-isomer via diastereomeric excited-state complexes of the substrate with a chiral sensitizer, and taken as evidence in support of the same enantiodifferentiation mechanism operative in all the solvents employed [46–48]. In the present case, the effective enantio-differentiating step is likely to be switched in the middle of temperature range employed (the origin of which will be discussed in the sections to follow). Nevertheless, no obvious deviation or kink is seen in the regression line (Fig. 3), which is hard to rationalize if the enantio-differentiation mechanism suffers significant changes. Therefore, it is reasonable to conclude that the same enantio-differentiation mechanism, involving the interaction of prochiral KE with Ni-TA as a major driving force, operates for all the substrates and over the entire temperature range upon catalytic hydrogenation with TA-modified Ni powder and with TAmodified Raney Ni as well.

It is interesting to further discuss the origin of the different driving forces for determining the enantio-selectivity upon hydrogenation over modified Ni powder versus Raney Ni. Thus, the high enantio-selectivity is driven by negative $\Delta\Delta H^{\ddagger}$ in the modified Raney Ni case, but by positive $\Delta\Delta S^{\ddagger}$ in the low temperature region and by negative $\Delta\Delta H^{\ddagger}$ in the high temperature region in the modified Ni powder case. One of the plausible explanations for this apparent switching of the determinant activation parameter is that the optimum temperature for giving the highest *e.e.* is in the middle of the experimental temperature range in the Ni power case, but is much lower for the RNi catalyst due to its higher hydrogenation activity.

3.3. Enantio-differentiation mechanism

In general, the enantio-differentiation mechanism operative in heterogeneous catalysis is apparently more complicated than that in homogeneous catalysis. However, the essential process(es) that determine the product's *e.e.* do not essentially differ. Thus, in both the homogeneous and heterogeneous catalyses, the intermediate associated with the enantio-differentiation is a pair of diastereomeric catalyst-substrate complexes formed either in isotropic solution or on solid surface. Thus, the difference in activation free energy ($\Delta\Delta G^{\ddagger}$) between the diastereomeric complex pair, precursor to the (*R*)- and (*S*)-products (Fig. 1), is the only determinant in both the cases.

Although a general mechanism for the enantio-differentiating hydrogenation over TA-modified Raney Ni has already been proposed by Tai et al. [6] and also by our research group [42] (Fig. S2), these models do not fully explain the effect of hydrogenation temperature on the enantio-selectivity. The present catalytic system, which employs apparently similar TA-modified Ni powder as catalyst but exhibits the unprecedented temperature-dependence behavior of enantio-selectivity, enabled us to examine this mechanism more closely based on the effect of the hydrogenation temperature on *e.e.* Indeed, as discussed above, the same enantio-differentiation mechanism is considered to operate in the high and low temperature regions despite the opposite temperature-dependence of *e.e.* observed in these two regions (*vide supra*). We now propose a mechanism compatible with all the experimental results obtained in the past and present studies on the enantiodifferentiating hydrogenation with TA-modified Ni catalysts. Scheme 2. Reaction mechanism for the enantio-differentiating hydrogenation of KE to (*R*)- and (*S*)-HE over TA-modified Ni catalyst (Ni-TA), which proceeds through a pair of diastereomeric complexes [Ni-TA-*re*-KE] and [Ni-TA-*si*-KE] followed by the attack of hydrogen generated on Ni surface (Ni-H) and subsequent spontaneous desorption of produced HE from the surface.

In the initial stage, prochiral KE is adsorbed and activated on the Ni surface by forming a pair of the diastereomeric hydrogen-bonding complexes with TA immobilized on Ni, *i.e.*, [Ni-TA-*re*-KE] and [Ni-TA-*si*-KE], which in turn expose the enantiotopic *re*- and *si*-face to the bulk solution. Subsequently, the attack of hydrogen on nickel surface (Ni-H) occurs from the opposite face to give (*R*)- and (*S*)-HE, respectively (Scheme 2). Similar reaction scheme has already been proposed for the hydrogenation over heterogeneous [49] and homogeneous catalysts [50]. The diastereomeric complexes are in equilibrium with free KE at the forward rate constant k_1^{re} or k_1^{si} , and backward rate constant k_1^{re} or k_1^{si} .

The steady-state approximation applied to the intermediate complex of prochiral KE with TA on Ni surface leads to the general Eq. (3) for the *e.r.* value of HE produced.

$$e. r. = \frac{[R]}{[S]} = \frac{v^R}{v^S} = \frac{k_1^{re}}{k_1^{si}} \cdot \frac{(k_{-1}^{si} + k_H^{si}[\text{Ni-H}])}{(k_{-1}^{re} + k_H^{re}[\text{Ni-H}])} \cdot \frac{k_H^{re}}{k_H^{si}} \cdot \frac{k_d^R}{k_d^S}$$
(3)

where the dissociation rate constants of both enantiomers from the catalyst surface, k_d^R and k_d^S , are also taken into consideration. The last term is practically close to unity $(k_d^R/k_d^S \approx 1)$ and hence negligible, as the enantioselectivity is not dependent on the conversion and no product inhibition was observed in all the examined cases. This general equation can be further simplified in different ways in the low and high temperature regions as detailed in the following sections for better understanding of the factors and mechanism that control the enantioselectivity in these two regions.

3.3.1. Enantioselectivity in the high temperature region (373–393 K)

At higher temperatures, KE bound to TA-Ni is more rapidly consumed by the attack of hydrogen on the Ni surface and the dissociation constant of KE-TA complex becomes negligible in the rate equation; *i.e.*, $k_1^{re} < k_H^{re}$ [Ni-H] and $k_1^{si} < k_H^{si}$ [Ni-H]. Under such a condition, the Eq. (3) is reduced to Eq. (4), which indicates that the enantioselectivity is determined solely by the relative rate of complex formation.

$$e.\ r. = \frac{k_1^{re}}{k_1^{si}} \tag{4}$$

The validity of this equation has been experimentally confirmed for the enantio-differentiating hydrogenation of methyl acetoacetate over Raney Ni catalyst modified with chiral amino acids and hydroxyalkanoic acids in a kinetic study [49], where the apparent hydrogenation rate constants for the conversion of adsorbed KE to the both HE enantiomers were demonstrated to be comparable. If this is also the case with the hydrogenation over TA-modified Ni powder in the high temperature region, the differential activation parameters obtained experimentally (Table 2) should belong to the initial complex formation process (Eq. (4)). Thus, the (R)-preference observed is kinetic in origin $(k_1^{re}/k_1^{si} > 1)$ and ascribed to the large negative (favorable) $\Delta \Delta H^{\dagger}$ values despite the entropic drawback ($\Delta\Delta S^{\ddagger} < 0$). This is the cause that lowers the enantio-selectivity when the hydrogenation temperature is elevated in the high temperature region (Fig. 2). The kinetic (R)-preference is likely to originate from the thermodynamic stability of intermediate complex [Ni-TA-re-KE] compared to that of [Ni-TA-si-KE], as depicted in Fig. 1.

3.3.2. Enantioselectivity in the low temperature region (343–363 K)

At lower temperatures, the hydrogen addition to adsorbed KE slows down and the pre-equilibrium between free and adsorbed KE is established; i.e., $k_{-1}^{re} > k_{H}^{re}$ [Ni-H] and $k_{-1}^{si} > k_{H}^{si}$ [Ni-H]. Then, the Eq. (3) is reduced to Eq. (5) as follows.

$$e. r. = \frac{k_1^{re}}{k_1^{si}} \cdot \frac{k_{-1}^{re}}{k_{-1}^{re}} \cdot \frac{k_{\rm H}^{re}}{k_{\rm H}^{si}} = \frac{K^{re}}{K^{si}} \cdot \frac{k_{\rm H}^{re}}{k_{\rm H}^{si}}$$
(5)

This indicates that the enantioselectivity is governed both thermodynamically and kinetically by the relative complex stability (K^{re}/K^{si}) and the relative rate of hydrogen addition $(k_{\rm H}^{re}/k_{\rm H}^{si})$.

In this region also, the catalytic hydrogenation over TA-modified Ni powder leads to the predominant formation of (R)-HE, which is however driven by the positive $\Delta\Delta S^{\ddagger}$ (Table 2). Hence, the enantioselectivity is enhanced by increasing the hydrogenation temperature (Table 1), as $\Delta \Delta G^{\ddagger} = \Delta \Delta H^{\ddagger} - T \Delta \Delta S^{\ddagger}$, where consistently $\Delta \Delta H^{\ddagger} < T \Delta \Delta S^{\ddagger} (\Delta \Delta H^{\ddagger} \ge 0,$ $\Delta\Delta S^{\dagger} > 0$). However, the origin of the positive $\Delta\Delta S^{\dagger}$ is not immediately assignable to a single cause, as the enantioselectivity is a function of two factors, *i.e.*, K^{re}/K^{si} and k_{H}^{re}/k_{H}^{si} . On the basis of the accepted complexation models for (R,R)-TA-modified Raney Ni catalysis [6,42] and the fact that (R)-HE is predominantly produced in the present catalytic hydrogenation, the [Ni-TA-re-KE] complex precursor to (R)-HE is considered to be more stable than the [Ni-TA-si-KE] complex due to its favorable conformation to build stronger hydrogen-bonding and/ or ion-dipole interactions of KE with Ni-TA (where TA is adsorbed as sodium salt of tartaric acid [51,52]). The more stable complex is conformationally better defined (more rigid) with lesser freedoms and hence its formation, though driven by the enthalpic gain from the above-mentioned interactions, should be inherently less favored by entropy. Therefore, the complexation step is not likely to be the origin of positive $\Delta\Delta S^{\ddagger}$ observed for the present system. Instead, the conformationally more rigid [Ni-TA-re-KE] intermediate, rather than the more flexible [Ni-TA-si-KE] complex, will gain additional freedoms in the transition state upon subsequent hydrogen attack, affording a positive $\Delta\Delta S^{\dagger}$ value, as observed experimentally (Table 2).

4. Conclusions

In the present study, the enantio-differentiating hydrogenation of a series of alkyl 3-oxobutanoates over TA-modified Ni powder catalyst was examined at the temperatures ranging from 333 to 393 K. The enantioselectivity of alkyl 3-hydroxybutanoates produced was not a simple function of the hydrogenation temperature to afford a bent Eyring plot with the highest (ceiling) enantioselectivity of 91-94% e.e. attained at 363-373 K for all the substrates. Nevertheless, the differential activation parameters derived from the enantioselectivities obtained in both the low and high temperature regions for TA-modified Ni powder and Raney Ni catalysts exhibited a nearly perfect enthalpyentropy compensation. The compensation effect observed indicates that a common enantio-differentiation mechanism operates for all the substrates and Ni catalysts over the entire temperature range employed. The slope and intercept of the regression line enabled us to gain indepth insights into the factors and mechanism that control the catalytic hydrogenation over the chirally modified Ni catalysts. The results and concept obtained in this study allow us further rational design of heterogeneous catalytic systems.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mcat.2018.02.023.

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