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Enhanced enantioselectivity in the heterogeneous catalytic hydrogenation of acetoacetate esters into the corresponding 3-hydroxybutyrates using commercial nickel powder

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ABSTRACT

Heterogeneous catalytic hydrogenation of acetoacetic acid esters over tartaric acid/NaBr-modified Ni powder was determined to be a critical function of the steric bulk of the ester moiety to afford quantitatively 3-hydroxybutyrate in 94% enantiomeric excess when ethyl and *i*-butyl esters are used, providing a facile route to optically active 3-hydroxybutyrates.

1. Introduction

Chirality is one of the most essential issues in living organisms due to the asymmetric nature of basic molecular building blocks such as amino acids and sugars. As a consequence, the majority of metabolic reactions involve chiral compounds. One such molecule is (*R*)-3-hydroxybutyrate, which is a member of the so-called 'ketone bodies'. Hydroxybutyrate is involved in the ketogenesis process in liver mitochondria, and acts as an energy source for many peripheral tissues, particularly in the heart, skeletal muscle, and brain in the case of glucose starvation.[1–3] Therefore, its blood level is an important diagnostic tool for monitoring various pathological conditions. Furthermore, hydroxybutyrate serves not only as a component of biodegradable plastics that are used in tissue engineering,[4–6] but also as a chiral building block for the synthesis of a wide variety of fine (bio)chemicals, such as antibiotics,[7–10] pharmaceuticals,[11–13] and nutritional supplements,[12,14] as well as being a component for improving drug delivery to the brain.[15]

Currently, there are several main approaches to synthesize enantiopure hydroxybutyrate, which include bacterial depolymerization of poly(hydroxyalkanoate),[16] biosynthesis from glucose,[17] enzymatic reduction of β-ketoesters,[18] and asymmetric catalytic hydrogenation of β-ketoesters.[19,20] Of these biological and chemical routes to hydroxybutyrate, the last one, in particular heterogeneous catalysis, seems to be the most promising for industrial application for the following reasons: the facile preparation, easy separation, convenient recovery, and reuse of the catalyst, as well as the use of economically and environmentally benign procedures. In general, in the case of heterogeneous enantio-selective catalysts, the most systematically studied systems that give high enantioselectivities are Pt[21–23] and Pd[24,25] modified with cinchona alkaloids and Ni modified with tartaric acid. For the purpose of obtaining hydroxybutyrate, the most suitable catalytic system is the last one. In this catalytic system, the chiral catalyst is prepared by modifying Raney or metallic Ni with tartaric acid and NaBr is conventionally used. The best result obtained thus far was achieved in the case of modified metallic Ni by systematically examining the Ni source and modifying the hydrogenation conditions for methyl acetoacetate to afford quantitatively methyl hydroxybutyrate with up to 91% enantiomeric excess (ee).[26] This type of catalyst has two additional advantages for its use in industry; it does not require the less reproducible dissolution of an Al–Ni alloy (in the case of Raney Ni) or the somewhat dangerous pre-activation by hydrogen gas at elevated temperatures,[27] and still retains its original hydrogenation activity and enantiodifferentiation ability for 3 months.[28] The only drawback of this catalyst is the enantioselectivity upon hydrogenation, which is not high enough for pharmaceutical applications (95% ee).[29] Herein we report a convenient, highly efficient, and versatile technique for obtaining enantiomeric hydroxybutyrate with up to 94% ee by carefully choosing the steric bulk of the ester moiety of the substrate in the catalytic hydrogenation over tartaric acid-NaBr/Ni under the optimized conditions (see Scheme 1 and Section 4).

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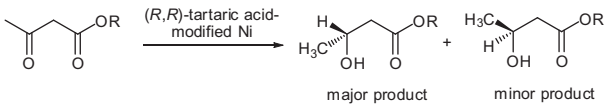

Scheme 1. Enantiodifferentiating hydrogenation of normal and branched alkyl and aryl acetoacetates to the corresponding (*R*)-3-hydroxybutyrates over a chiral Ni catalyst prepared by directly modifying commercially available Ni powder with (*R*,*R*)-tartaric acid and NaBr without any pre-treatment (for R, see Table 1).

2. Results and discussion

One of the key steps in the catalytic hydrogenation is the enantiotopic face-differentiating supramolecular complexation of prochiral acetoacetate with enantiomeric tartaric acid adsorbed on the Ni surface, which is followed by the asymmetric hydrogenation of the carbonyl group in acetoacetate with activated hydrogen on the Ni surface.[19] Of these two successive key processes, the first one plays the dominant role in determining the product's ee. In general, the geometry and stability of chiral supramolecular systems are affected by several factors, including the relative size of the complexation partners,[30–32] and hence the steric bulk and conformation of the substrate molecule should play important roles upon adsorption on the Ni surface as well as the subsequent enantiomeric face-differentiating hydrogenation. Indeed, some of these effects have been observed upon catalytic hydrogenation of homologous acetoacetate derivatives over chirally modified Raney Ni.[19,33,34] However, since biologically important enantiopure hydroxybutyrate is of our prime interest herein, a series of branched and unbranched alkyl, as well as benzyl acetoacetate were employed as prochiral substrates for examining their steric and electronic effects on the enantiodifferentiating hydrogenation over tartaric acid/NaBr-modified Ni powder to generally afford considerably high ee values. The catalytic reaction was carried out at two different temperatures, that is, 100 and 110 °C, which are known to be optimal for the hydrogenation of methyl acetoacetate over the modified Ni powder catalyst in terms of the yield and ee,[26] to give the results shown in Table 1, where the corresponding data obtained by using conventional modified Raney Ni catalyst[19,33,34] are included for the sake of comparison.

The acetoacetate substrates used herein were divided into three main categories according to the branching of the ester group: 1°, 2°, and 3°, see Table 1. Within the same category, the ester groups of different chain lengths were employed. Methyl acetoacetate, which belongs to the first category and has been used as a benchmark substrate of this type of catalytic reaction, was hydrogenated to give methyl (*R*)-hydroxybutyrate in 100% conversion and 91% ee and 89% ee at both 100 and 110 °C, respectively, which was in good agreement with the literature.[26] It should be noted that the ee value obtained with this catalyst is consistently higher by 5% than that of the Raney Ni-based catalysts, thus reflecting the enhanced enantio-differentiating efficiency of metallic Ni powder.

As can be seen from Table 1, further elongation and branching of the alkyl ester chain significantly influenced the catalytic performance of the Ni powder, which is in sharp contrast to the relatively modest effect in the case of Raney Ni. Thus, the conversion at 100 °C gradually decreased from 100% to 97% and then rather suddenly to 85–78% by elongating the alkyl group from Me to Et and then to Pr and Bu, but was not affected by incorporating an aromatic group (100% conversion). Alkyl branching had a very similar effect. The *i*-Bu ester with remote branching (1° group) resulted in a slight decrease in the conversion to 96%, while α

Table 1
Comparison of the enantiodifferentiating hydrogenation over tartaric acid/NaBr-modified Ni powder versus tartaric acid/NaBr-modified Raney Ni catalysts

Ester group (R)		*T* (°C)	Ni powder[a]				Raney Ni[b,c,d]			
			Conv. (%)	ee (%)	Δee[e] (%)	Δee[f] (%)	Conv. (%)	ee[g] (%)	Δee[e] (%)	Ref
1°	CH_3	60					h	86	≡0	b
		100	100	91	≡0	+5	98	86	≡0	d
		110	100	89	≡0					
	CH_2CH_3	85					97	87		d
		100	97	94	+3	+6	h	88	+2	c
		110	94	92	+3					
	$CH_2CH_2CH_3$	100	85	92	+1	+4	h	88	+2	c
		110	100	91	+2					
	$CH_2(CH_2)_2CH_3$	100	78	93	+2	+5	h	88	+2	c
		110	100	91	+2					
	$CH_2CH(CH_3)_2$	100	96	94	+3	+6	95	88	+2	d
		110	100	92	+3					
	$CH_2C_6H_5$	100	100	89	−2					
		110	100	88	−1					
2°	$CH(CH_3)_2$	60					h	87	+1	b
		100	96	92	+1	+4	95	88	+2	d
						+7	h	85	−1	b
		110	100	91	+2					
	$CH(CH_3)CH_2CH_3$[i]	100	80	91	0					
		110	100	93	+4					
	$CH(CH_2CH_3)_2$	100	84	92	+1					
		110	100	93	+4					
3°	$C(CH_3)_3$	60					h	88	+2	b
		100	77	84	−7		h	84	−2	b
		110	64	72	−17					

[a] This work.
[b] Ref. 25.
[c] Ref. 33.
[d] Ref. 34.
[e] Difference in ee relative to the value obtained for methyl acetoacetate substrate at an identical temperature with the same catalyst.
[f] Difference in ee relative to the value obtained for methyl acetoacetate with Raney Ni catalyst at an identical temperature (100 °C).
[g] Some of the values are calculated based on the specific rotation measurements and reported values of maximum optical rotation of the corresponding isomers.
[h] Not reported.
[i] A racemic substrate was used. The ee values were calculated based on the chirality of the β-carbon of 3-hydroxybutyrate.

branching (2° group) led to 96–80% conversion, depending upon the alkyl chain length. However, raising the temperature to 110 °C significantly increased the conversion in almost all examples. The sterically more demanding *t*-Bu group (3° group) considerably decelerated the reaction down to 64% conversion at 110 °C. In sharp contrast, Raney Ni-based catalysts are known to give almost identical conversions of 95–98%, irrespective of the substrate structure.[34] These observations could be attributed to the difference in surface morphology between the Ni powder[26] and Raney Ni,[35] which leads to the structural selectivity due to the distinct accessibility of substrate to the catalyst surface where the corresponding hydrogenation reaction takes place. This conclusion is compatible with the hydrogenation mechanism proposed previously for tartaric acid/NaBr-modified Ni catalyst,[19] in which the substrate is held near the catalyst surface through hydrogen-bonding interactions with tartaric acid anchored to the Ni surface.

The effect of the alkyl chain length and branching on enantioselectivity is somewhat less pronounced but is noticeable. In particular, the ee value was appreciably improved from the original 89–91% for Me to 92–94% upon elongation to Et and to 91–93% upon further elongation to *n*-Pr and *n*-Bu. This trend may be attributed to the ambivalent roles of the steric bulk in enhancing the enantiomeric face-selectivity upon complexation and subsequent hydrogenation and also discouraging the tight complexation with tartaric acid, which would be balanced when the Et ester is used. This view may be rationalized by the fact that the more bulky *i*-Pr group yields a reduced 91–92% ee, while the more bulky *t*-Bu ester gives the lowest 72–84% ee. For secondary branched short alkyl esters, no such unfavorable effect on the enantioselectivity was observed. Thus, the *n*-Pr and *i*-Pr esters afforded comparable 91–92% ee, while *i*- and *s*-Bu esters gave slightly higher 92–94% and 91–93% ee, respectively. The introduction of the aromatic substituent also reduces the ee value down to 88–89%, indicating that the π-interactions do not play any significant role in the stabilization of the supramolecular complex or the asymmetric attack of an activated hydrogen molecule, while excessive bulk discourages the prochiral faceselectivity of the supramolecular complex. This bulkiness-controlled enantioselectivity is in contrast to the almost invariant ee values (Δee = ±2%) regardless of the ester structure, which have been reported for the Raney Ni catalyst (Table 1). Furthermore, the sensitivity to steric bulk observed for the Ni powder-based catalyst allowed for considerable enhancement of the enantiodifferentiating performance of catalytic heterogeneous hydrogenation by 6–7% in comparison with the conventional Raney Ni-based catalysts.

So far, there have been several models proposed for the intermediate host-guest complex of chiral tartaric acid with prochiral acetoacetate substrate on the metallic surface.[36] For example, according to Tai's mechanism, the two hydroxyl groups of the tartaric acid molecule attached to the Ni surface interact with two carbonyl groups of the β-ketoester via hydrogen bonding.[37] Meanwhile, Osawa et al. proposed a different type of interaction between tartaric acid and β-ketoester. In this case the carbonyl group of the β-ketoester interacts with one hydroxyl group of tartaric acid, while the ester carbonyl moiety is bonded to sodium ion, which is an important component of the reaction mixture to ensure high enantioselectivity of hydrogenation.[38] However, none of these reports explicitly explain the role of substrate bulk in general and in particular the effect of the ester substituent on the catalytic efficiency. Although the specific host–guest interaction mechanism and the role of the ester group in the activated catalyst complex are yet to be understood in detail, the results obtained clearly indicate that the most plausible rationale of the observed behavior is a structural 'key-and-lock' principle based upon the geometrical complementarity between the adsorbed tartaric acid and acetoacetate derivative resulting in the definite enantioface-selective fixation of the prochiral substrate for the unidirectional approach of activated hydrogen.

3. Conclusion

In conclusion, high enantioselectivities of up to 94% have been achieved in enantiodifferentiating heterogeneous catalysis over chirally modified Ni and by judicious choice of the prochiral substrate. These results pave the way to the facile industrial production of biologically important enantiopure hydroxybutyrate derivatives.

4. Experimental

Nickel powders (5 μm) purchased from Aldrich were directly subjected to chiral modification without any pretreatment, such as hydrogen activation. The chiral modification was performed under the conditions optimized previously for this type of catalyst.[26] Thus, the non-activated nickel powders (0.5 g) were immersed in an aqueous solution (50 cm^3) of (*R*,*R*)-tartaric acid (0.5 g) and NaBr (2.0 g) at 100 °C, the pH of which was pre-adjusted to 3.2 with an aqueous 1 M NaOH solution. NaBr was added to the modification solution to block the non-enantiodifferentiating sites of tartaric acid/Ni catalyst, thus preventing the generation of racemic products.[39] After immersion for 1 h, the modification solution was removed by decantation and the catalyst was successively washed once with deionized water (10 cm^3), twice with methanol (25 cm^3), and twice with tetrahydrofuran (THF) (10 cm^3). The modified catalyst was added to a mixture of alkyl acetoacetate (43 mmol for methyl ester and 21.5 mmol for other esters), acetic acid (0.1 g), and THF (10 cm^3) placed in an autoclave equipped with a magnetically coupled mechanical stirrer. The hydrogenation was run for 20 h at 100 or 110 °C and at a hydrogen pressure of 9 MPa. The hydrogenation product, a mixture of alkyl (*R*)- and (*S*)-3-hydroxybutyrates, was isolated from the reaction mixture by distillation. The conversion was determined by gas-liquid chromatography (GLC) on a GL Science model GC-4000 equipped with a CP Chirasil DEX-CB capillary column (0.25 mm × 25 m) at 90 °C, while the enantioselectivity was determined by chiral GLC after acetylation of the reaction product using acetyl chloride and pyridine. A portion of the acetylated sample was subjected to the chiral GLC analysis on a CP Chirasil DEX-CB column (0.25 mm × 25 m) operated at 90 °C. The ee value was calculated from the peak integration of the corresponding enantiomer peaks. The reproducibility of the ee value was found to be within ±2%.

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