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Catalytic asymmetric synthesis of β-hydroxyacids and their esters

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Contents

I.	Introduction	329
II.	Optically active biodegradable polymers based on β-hydroxyesters	329
III.	β-Hydroxyacid esters as chiral synthons	331
IV.	Enzymic synthesis of β-hydroxyacids and β-hydroxyesters	331
V.	Synthesis of β-hydroxyesters by the hydrogenation of ketoesters on heterogeneous dissymmetric catalysts	333
VI.	Synthesis of optically active β-hydroxyesters by the hydrogenation of ketoesters on metal complex catalysts with chiral ligands	342
VII.	Conclusion	342

Abstract. Data on the catalytic methods for the reduction of β-ketoacids and their esters to the corresponding optically active hydroxyacids and hydroxyesters with the aid of enzymes and chiral heterogeneous and metal complex catalysts are surveyed. The application of optically active hydroxyesters as chiral synthons and monomers for the synthesis of biodegradable polymers is examined. Procedures for increasing the optical purity of the products are outlined on the basis of an analysis of the literature data and the author's own results. The bibliography includes 151 references.

I. Introduction

Optically active carboxylic hydroxyacids and their esters are key intermediates in the biosynthesis and metabolism of aliphatic acids, which are widely distributed in biological systems. A number of chiral lower homologues of hydroxyacids are used as chiral synthons in asymmetric syntheses of natural products and medicinal preparations. The efforts of many investigators have therefore been directed towards the search for new effective methods of synthesis of the most important α- and β-hydroxyacids and their esters and to the improvement of the already known procedures for their synthesis by the enzymic reduction of ketoacids[1,2] or by the hydrogenation of the keto-group with the aid of chiral heterogeneous and homogeneous catalysts.[3,4]

Optically active hydroxyacid esters have also attracted special attention as promising chiral monomers for the synthesis on an industrial scale of biodegradable polymers, for example of the type Biopol (Zeneca Company, Great Britain).

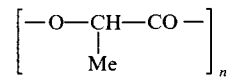
Despite the interest shown in the development of methods of synthesis of chiral β-hydroxyacids and their esters, publications giving a compilation of data on the methods of synthesis of these compounds together with their critical assessment are so far lacking in the literature, although the increasing number of publications has led to an urgent need for such a survey. In the present review, an attempt is made to fill this gap. Studies carried out during the last ten years are mainly analysed. The analysis considers principally the most thoroughly developed methods: the reduction of ketoacids and their esters by the enzymic procedure and with the aid of heterogeneous metallic catalysts modified by optically active compounds. Less attention has been devoted in the literature to the application of highly effective chiral metal complex hydrogenation catalysts and one can only hope for a development of this aspect in the future.

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II. Optically active biodegradable polymers based on β-hydroxyesters

Optically active polycondensation polymers are known to have higher melting points (softening temperatures), higher degrees of crystallinity, and better mechanical properties than racemic polymers by virtue of the stereoregularity of their structure. For example, the optically active polylactide



is significantly superior to the corresponding polymer based on the racemate as regards characteristics such as crystallinity, melting point (< 449 K), and insolubility in a number of solvents, these characteristics improving with increase in the optical purity of the polymer.[5,6]

Polycondensation polymers based on carboxylic β-hydroxyacids and their esters, which participate in the metabolism of a number of microorganisms and decompose when acted upon by soil bacteria, have aroused particular interest. These polymers constitute an ideal environmentally clean material for the manufacture of polymeric articles because they decompose biologically in waste after use.

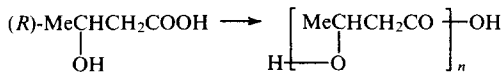
An optically active polycondensation polymer is formed from (*R*)-(−)-β-hydroxybutyric acid (HBA) or its esters when they are acted upon by a number of microorganisms. It can also be obtained by reducing ketoacids or the corresponding esters in the presence of enzymes and heterogeneous or metal complex catalysts.[7,8] In a number of papers published after the first communication about the synthesis of poly(hydroxybutyric acids) (PHBA) from HBA,[9] the properties of this lipid-like

polymer are examined[10] (the microbiological preparation of PHBA has been surveyed[11]).

The polymer PHBA, accumulating in the cells of bacteria of a particular species, serves as an energy storage material and plays the same role as starch in plants.[12,13] The polymer, containing on average 138 000 units, can be isolated from the bacterial mass in the form of hydrophobic 0.5 μm grains. A polymer with a molecular mass from 60 000 to 1 000 000 (100–10 000 HBA units) can be formed, for example, when the system is acted upon by hydroxybutanolide-Co-A-polymerase. The PHBA–PHVA copolymer is formed from a mixture of HBA and β-hydroxyvaleric acid (HVA).

PHBA can be obtained by the usual fermentation methods using laboratory equipment.[14] Cell material containing up to 70% of PHBA is obtained by the fermentation of a 24% aqueous solution of fructose acted upon by *Bacto Nutrient Broth* (Difco). Pure PHBA is isolated by extracting the biomass in a Soxhlet extractor with chloroform and is precipitated by adding ether. This laborious procedure involves filtration for many hours and treatment of the solutions, which requires the consumption of large amounts of solvents. For example, 5 litres of acetone has to be consumed in order to obtain 35 g of PHBA.

The polymer obtained, consisting of (*R*)-(−)-HBA units, has a 'head to tail' linear structure.[12]



The polyester, namely poly(ethyl β-hydroxybutyrate) (PEHB), is a crystalline substance with a right-handed helical structure[15,16] and weak optical activity. This polymer exhibits a positive Cotton effect at a wavelength of 215 nm (in ethanol).[13,14]

In solution in chloroform and dichloroacetic acid, the PEHB structure is analogous to that of proteins (helix–coil). For certain proportions of the solvents, maintaining or loosening the helical structure of the polymer (dichloroacetic acid and ethylene dichloride), there is a sharp jump in optical activity. A similar jump, corresponding to the helix–coil transition at 351 K, is also observed as the temperature is increased (Fig. 1). With increase in molecular mass, the melting point rises from 350 to 473 K. The polymer is insoluble in water, methanol, and dimethylformamide (DMF).

Thermal instability and sensitivity to the action of acids and bases are characteristic of PEHB. It is thermoplastic and may be used in the form of films, fibres, etc. A valuable property of this polymer is its susceptibility to biodegradation. The PEHB–PEHV copolymers, which began to be produced by British companies (ICI, Zeneca, Marlborough Biopolymers Ltd) in 1986, are of considerable interest.[7]

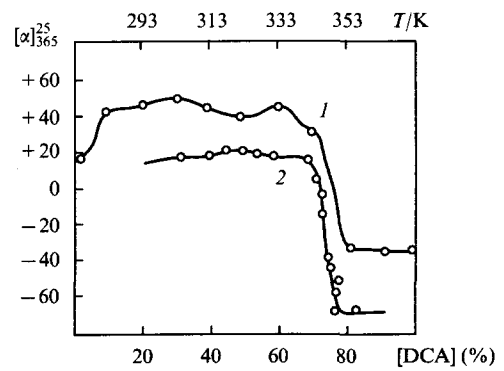
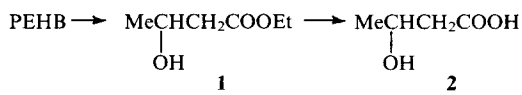
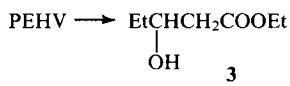


Figure 1. Dependence of the specific rotation $[\alpha]^{25}_{365}$ of the PEHB polymer on the solvent composition in the dichloroacetic acid (DCA)–methylene dichloride (EDC) system (*1*) and on temperature in the 76 : 24 DCA : EDC mixture (*2*) according to the data of Marchesault et al.[12]

Publicity announcements in the scientific and popular chemical literature of the 1980s convey the sensational nature of the discovery of these new polymers: 'Artificial polymeric materials from bacteria',[17] 'A new procedure for the development of polymers based on bacteria',[18] 'Back to nature — the beginning of a new era of biopolymers',[18] etc. The (*R*)-EHB–(*R*)-EHV copolymer with different monomer ratios can be obtained in yields up to 80% by the controlled fermentation of glucose or fructose by the bacteria *Alcaligenes eutrophus*,[19,20] *Hydrogenomonas eutropha*,[20] or *Bacto Nutrient Broth*.[14]

By depolymerising the copolymer produced, for example, by ICI under the name Biopol TM, it is possible to obtain in a high chemical yield (y) the corresponding monomeric optically pure esters and, after their hydrolysis, also the optically pure β-hydroxyacids.[20–22] For this purpose, the crude cell material, containing up to 70% of PEHB, is treated with $Ti(OEt)_4$ in ethanol and heated for 2 h at 388–433 K. The mixture is filtered, the solvent eliminated, and the product, (*R*)-(−)-EHB **1**, is distilled. The yield is 75%. The acid (*R*)-(−)-HBA **2** is obtained by the hydrolysis of EHB with 1 M KOH at 273 K.





The chemical yields and specific rotations of the optically pure β-hydroxyacids and their esters obtained in this way are presented below in Table 1.

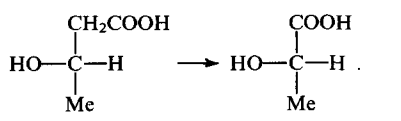
Table 1. Optical characteristics of certain β-hydroxyacids and their esters.

Compound	T_b/K (P/Pa)	T_m/K	$[\alpha]^T_D$ [a]/deg	y (%) (OY)[b]	Ref.
1	353 (2100)	–	−43.2 (*c* 5, chloroform)	90	20–22
2	358–360 (10)	315–317	−24.5 (*c* 5, chloroform)	93	20–22
5	–	316–319	−25.0 (*c* 6, water)	(98)	19, 28
3	363 (2000)	–	−34.5 (*c* 5, chloroform)	65	20–22
4	333 (20)	–	−19.0 (*c* 2.7, chloroform)	94	1

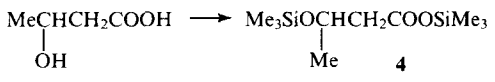
[a] Here and henceforth this formulation means that the specific rotation $[\alpha]^T_D$ has been measured at the given temperature and wavelength (589 nm, Na D-line) in the solvent indicated (chloroform, water, etc.) at a concentration c expressed as the number of grams of the compound under consideration (1 g of EHB, 5 g of HBA, etc.) in 100 ml of the *solution* in a layer 1 dm thick. [b] OY is the optical yield (%) defined as

$$OY = \frac{[R] - [S]}{[R] + [S]} 100.$$

Optically pure (*R*)-(−)- and (*S*)-(+)-HBA have been obtained by the resolution of the racemic acid via the quinine and strychnine salts.[21] The configuration of the acid (*S*)-(+)-HBA is genetically linked to that of (*S*)-(+)-lactic acid:



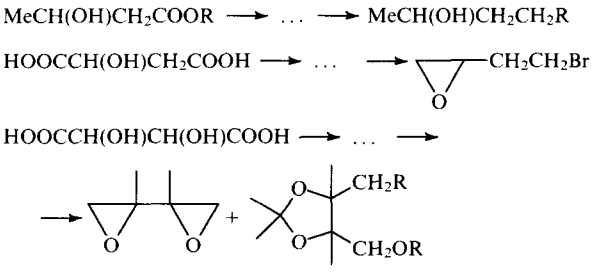
β-Hydroxyacid esters are unstable: during storage at room temperature, they give rise to oligomers, this tendency increasing in the series of esters Pr^i < Et < Me. Since the oligomerisation is catalysed by alkalies and acids, the ester to be stored must be carefully purified. The usual acetoacetic ester contains admixtures of dehydroacetic acid, methyl 3-acetoxypropionate, and diketene, which influence significantly the catalytic asymmetric hydrogenation of the ester.[23] For this reason, it is best to store EHB specimens in the form of the PEHB polymer or to convert HBA into the silyl ester **4**:[1,14,24-28]



The Fluka Company has suggested that the polymer (*R*)-PHBA be used as the starting material for the preparation of (*R*)-HBA **5** (Table 1)[19,28] and (*R*)-β-butyrolactone.[14,25,26]

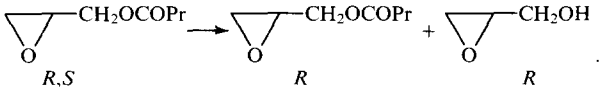
III. β-Hydroxyacid esters as chiral synthons

The molecules of β-hydroxyacids are extremely reactive, which makes it possible to obtain from them a wide variety of optically active derivatives and chiral synthons used in the synthesis of a number of medicinal preparations.[29,30] Certain examples of the successful use of optically active hydroxyacids as chiral synthons for the preparation of a number of chiral initial compounds are presented below.[31]



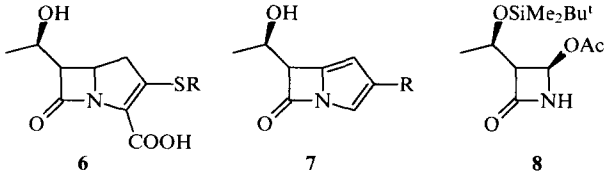
R = OTs, Br

The Andeno Company used PPL lipase for the kinetic resolution of the racemic glycidyl butyrate:[32]



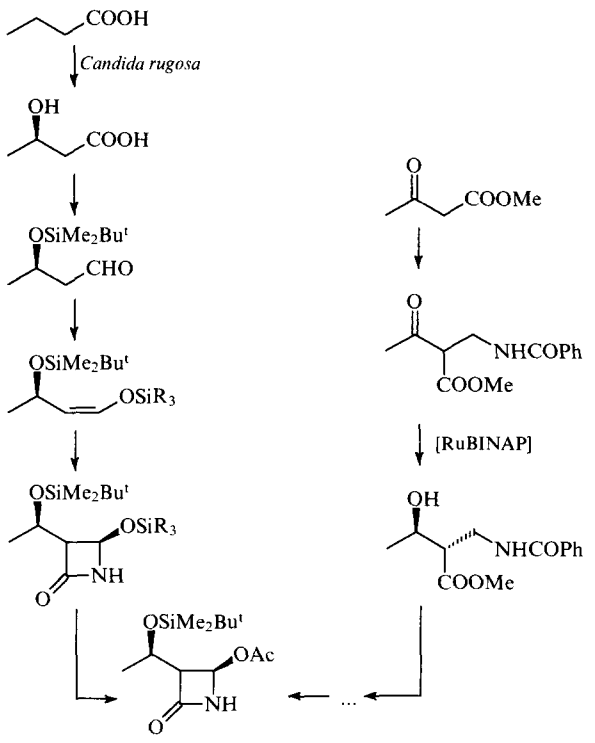
The Tagasago Company (Japan)[32] employs the chiral ruthenium complex [Ru-BINAP] [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl][34] in the reduction stage. In the latter case the azetidinone is obtained with *OY* = 98% and *de* = 95%.†

Antibiotics containing the β-lactam group belong to an important class of medicinal preparations. In the synthesis of carbapenem **6** and penem **7**, the key intermediate is the azetidinone **8**, which is synthesised in two ways.



6 **7** **8**

† The symbol *de* denotes an excess of the diastereoisomer and *ee* denotes an excess of the enantiomer, both expressed as percentages.



8

The acid (*R*)-HBA is used to synthesise a number of medicinal preparations. The depolymerisation of PHBA opens an easy path to the formation of the chiral synthon EHB, HBA, and a PHBA degradation product — the diol (*R*)-$MeCH(OH)CH_2CH_2OH$.[14] (*R*)- and (*S*)-2-Hydroxyglutaric acids have also become readily available. (*R*)-Isobutyl lactate is produced by the BASF Company. Carbomycin B,[35] (*R,R*)-pyrenophorin,[36] gramimycin A_1,[37] sulcatol,[2] lavandulol,[38] colletodiol,[37] and recifeiolid[39] belong to the class of medicinal preparations the structures of which contain a fragment of the chiral (*R*)-EHB molecule. (*R*)-β-Hydroxyiso-butyric acid, produced by the Kanegafuchi Company by the microbiological oxidation of isobutyric acid, can be used to synthesise the inhibitor captopril[40] via (*R*)-β-acetylmercaptoisobutyric acid, produced by the Andeno Company,[41] while its enantiomer, (*S*)-β-hydroxyisobutyric acid, is used in the synthesis of phytol — a fragment of the vitamin E molecule.[42,43]

IV. Enzymic synthesis of β-hydroxyacids and β-hydroxyesters

The bank of chiral natural optically active hydroxyacids consists of an extremely limited number of compounds: (*R*)- and (*S*)-lactic, (*R,R*)-(+)-tartaric, (*S*)-malic, and (*S*)-mandelic acids and their esters. The enzymic and catalytic asymmetric syntheses of these compounds therefore constitute an important source of chiral β-hydroxyesters. β-Hydroxyacids and β-hydroxyesters in the enantiomeric form are synthesised as follows:

by the kinetic resolution of the racemate with participation of a chiral auxiliary compound;[44]

by the depolymerisation of polyhydroxyesters or polyhydroxyacids;[14,45]

by the microbiological reduction of ketoesters with the aid of enzymes;[14]

by the catalytic hydrogenation of ketoesters on modified metallic catalysts;[3,4,46]

by the catalytic hydrogenation of ketoesters on chiral complex catalysts.[47]

The last three methods are of greatest interest.

The enzymic reduction of ketoesters to optically active hydroxyesters was first achieved with the aid of baker's yeast in 1918.[48] Although data[2,49] indicating a high effectiveness of this method were not subsequently confirmed,[50] its improvement made it possible to achieve an optical yield of EHB up to 85% and above,[45] while in a bioreactor (with continuous introduction of the substrate and aeration) the yield was up to 96%.[51] The method was developed further[52,53] and acquired preparative value mainly as a result of the studies by Seebach.[45,54] It proved possible to employ the reduction of ketoesters with the aid of baker's yeast (*Saccharomyces cerevisiae*) in practical organic synthesis.[32,51,54,55]

High *OY* values for the products are usually attained when the concentration of the substrate in the fermenting solution does not exceed 0.1%,[51] while the reaction time is 30–130 h. Under these conditions, the productivity of the process is 20–70 mg dm^{-3} h^{-1}. However, the need to employ large volumes of solutions, the long reaction time, the high consumption of sucrose (or another organic reducing agent — a hydrogen donor), the instability of the bacterial strain, the impossibility of the repeated employment of the reducing system, as well as the complexity of the isolation of the product prevent the wide scale employment of this method.[56,57] Furthermore, the selectivity of the enzymic reaction depends on a number of factors, such as the nature of the enzyme, the structure of the substrate molecule, and the reaction conditions.[58,59] For example, ketovalerate is reduced less effectively than ketobutyrate.[58,59]

According to the standard method for the reduction of acetoacetic ester [ethyl acetoacetate (EAA)] with the aid of baker's yeast,[45] the synthesis of 24 g of EHB from 40 g of EAA requires the consumption of 600 g of sucrose and 200 g of yeast and a vessel with a volume up to 5 litres has to be used. The reaction time is 134 h with a process productivity of 0.068 g dm^{-3} h^{-1}. The final product, (*S*)-(+)-EHB, is obtained in 59%–71% yield with $OY = 85\%$. A similar method is used to obtain BuHB ($OY \approx 90\%$).[14] The optical yield of HBA may be increased to 97% after several recrystallisations of the derivative EHB 3,5-dinitrobenzoate.[60] The optically pure EHB obtained had $[\alpha]_D = +43.5°$ (*c* 1, chloroform). The optical purity of EHB can be determined from the ^{19}F NMR spectrum of the ester comprising the Mosher reagent.[61]

An improvement in the method for the reduction of EAA also makes it possible to increase the optical yield of EHB to 95%. This is attained by the slow introduction of EAA into the fermenting solution under aerobic conditions.[51] The replacement of 5%–15% of sucrose in the fermenting solution by ethanol, glucose, fructose, glycerol, or mannitol[62] also helps to increase the *OY* of the hydroxyester.

Keeping the yeast in 5% aqueous ethanol for four days before use in the reaction helps to activate it and to raise the optical yield of the product to 95.9%.[63–65] According to the method of Ehrler et al.,[66] a suspension of 125 g of baker's yeast in 1 litre of 5% aqueous ethanol is stirred at 303 K for 4 days, after which 5 g of EAA is added. After 2–3 days, the reaction comes to an end (it is monitored with the aid of gas–liquid chromatography). The mixture is centrifuged and the filtrate is repeatedly extracted with ether for 4 days and the extract is vacuum distilled. EHB is obtained in 70% yield with $OY = 94\%$ and $[\alpha]_D = +40.9°$ (*c* 1, chloroform). Unfortunately this method does not yield satisfactory results when applied to other substrates, such as ketovalerate and fluorine-containing ketoesters. Only 2-formylbutanoate could be reduced to (*S*)-2-hydroxymethylbutanoate $HOCH_2CH(Et)COOEt$ in 70% yield with $OY = 95.5\%$. This product is an important chiral synthon analogous to the Roche acid $HOCH_2CH(Me)COOH$.[67] According to the data published by the Hoffmann La Roche Company, the latter product can be obtained with the aid of *Streptomyces griseu* with *OY* not exceeding 86.3%.[68]

A strain of the *Halobacterium halobium* bacteria reduces EAA to (*S*)-(+)-EHB with $OY = 44\%–76\%$, but the chemical yield of the product is low and the reduction is accompanied by hydrolysis of the ester to the acid. Hydrolysis of the racemic ester EHB with the aid of the above strain leads to (*R*)-(−)-EHB with $OY \approx 88\%$.[69]

The reduction of ketoesters with the aid of the thermophilic bacteria *Thermoanaerobicium brockii* (*Th.b.*) is carried out in the usual laboratory apparatus or in a bioreactor[70] by a procedure similar to that used in the case of yeast. However, this strain is sensitive to atmospheric oxygen and the reduction must be carried out under an argon atmosphere. In contrast to yeast, the strain reduces ethyl ketovalerate effectively to the β-hydroxyester ($OY = 93\%–97\%$).

Depending on the nature of the microorganism and the structure of the substrate molecule, products with the (*R*)- or (*S*)-configuration can be obtained by reduction of the ketoesters. Table 2 presents comparative data obtained for different substrates with the aid of baker's yeast and a strain of *Th.b.*[71] As can be seen, in certain cases the *Th.b.* strain is more effective than baker's yeast and, furthermore, makes it possible to obtain the other enantiomer of the hydroxyester.

Both enantiomers of the hydroxyacid may be obtained by reducing the ketoacid in the presence of NADH (reduced β-nicotinamide-adenine dinucleotide), bound to poly(ethylene glycol) in a membrane reactor.[72,73] The reduction of ketoesters in a nonaqueous medium (in solution in isopropyl hexadecanoate) by a suspension of a mixture of Asolectine phospholipids produced by the Fluka Company and yeast proceeds rather effectively (Table 3).[74]

Other examples of the influence of the structure of the substrate molecule and of the introduction of aromatic substituents or aromatic hexahydro-substituents into the ketoester $XCOCH_2COOR$ on the configuration of the enantiomers and diastereoisomers obtained[75] are presented in Table 4.

Apart from the asymmetric enzymic reduction of ketoesters to obtain optically active hydroxyesters from hydroxyacids, it is also possible to employ the enantioselective kinetic conversion of the hydroxyester racemate by the enzyme. Thus the DSM

Table 2. The influence of the structure of the β-ketoester and of the source of the enzyme on the optical yield and the absolute configuration of the β-hydroxyester formed.[70,71]

Initial ketoester	Hydroxyester obtained	Baker's yeast, 303 K		*Th.b.* strain, 345 K	
		configuration of product	*OY* (%)	configuration of product	*OY* (%)
EAA	EHB	*S*	97	*S*	80
$EtCOCH_2COOEt$	$EtCH(OH)CH_2COOEt$	*R*	40	*S*	84
$ClCH_2COCH_2COOMe$	$ClCH_2CH(OH)CH_2COOEt$	*S*	36	*R*	89
$PrCOCH_2COOEt$	$PrCH(OH)CH_2COOEt$	*R*	90	*S*	25
$HCOCH(Me)COOEt$	$HOCH_2CH(Me)COOEt$	*R*	60	*R*	72

Table 3. Reduction of β-ketoesters in solution in isopropyl hexadecanoate by a mixture of phospholipids and baker's yeast.[74]

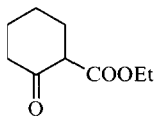
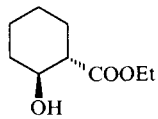
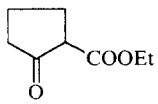
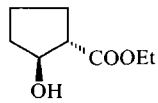
Ketoester	Hydroxyester	*OY* (%)	Reaction time /h	Enzyme : substrate mass ratio
$MeCOCH_2COOBu^t$	$MeCH(OH)CH_2COOBu^t$	91	96	10.6
F_3CCOCH_2COOEt	$F_3CCH(OH)CH_2COOEt$	58	120	11.8
		99	24	46.6
		99	19	14.0

Table 4. The influence of the substituents in the ketoester $XCOCH_2COOR$ molecule on the absolute configuration of the hydroxyester formed.

R	X	Configuration of hydroxyester	*OY* (%)	Microorganism	Ref.
Et	Me	*S*	97	yeast	51, 65
Et	Me	*S*	95	*C.Kluyveri*	50
Et	Ph	*S*	99	yeast	53
Et	CF_3	*R*	98	"	76
Et	CCl_3	*S*	98	"	76
Et	$ClCH_2$	*R*	99	*C.Kluyveri*	50
C_8H_{17}	$ClCH_2$	*R*	98	yeast	63
Et	$BrCH_2$	*S*	98	"	77
$PhCH_2$	N_3CH_2	*R*	95	"	77
K	CH_2OCH_2Ph	*S*	99	"	78
K	Me	*S*	100	"	52

Andeno Company has used successfully the lipase from *Pseudomonas fluorescens* for the kinetic resolution of the ester.[24] The product PhOCH(Et)COOEt is formed with $OY = 99\%$ and a conversion of 57%.[28]

Examples of the effective enantioselective resolution of other racemic hydroxyacids and hydroxyesters are known: thus, on treatment with *Candida rugosa*, the acid $HOCH_2CH(Me)COOH$ affords the (*R*)-product;[79] on treatment with chymotrypsin, the (*R*)-product is formed from $PhCH(OH)CH_2COOEt$ with $OY = 98\%$;[80] EtC(Me)(OH)COOMe is hydrolysed by esterase with formation of the (*S*)-product ($OY = 98\%$);[81] the product of the conversion of $MeCH(OH)CH(Me)COOEt$ by yeast has the (2*R*,3*S*)-configuration ($de = 86\%$ and $OY = 96\%$);[82] the asymmetric resolution of the $PhCH_2CH(OH)CH(Me)COOEt$ racemate on treatment with *P. farinosa* leads to the (2*R*, 3*S*)-product with $OY = 99\%$.[83]

β-Hydroxyesters can be obtained by reversible transesterification. The acid anhydride is used as the reversible acylating agent. When acted upon by PS lipase, it gives rise to the (*R*)-acid $PhCH_2CH_2CH(OH)COOH$ **9** in 39% yield and with $OY = 99\%$.[32]

The synthesis of chlorine- and fluorine-containing hydroxyesters by the reduction of the corresponding ketoesters effected by baker's yeast is of interest.[76]

$$Cl_3CCOCH_2COOEt \longrightarrow Cl_3CCH(OH)CH_2COOEt$$
S-**10**, ($y = 70\%$, $OY = 84\%$)

$$F_3CCOCH_2COOEt \longrightarrow F_3CCH(OH)CH_2COOEt$$
R-**11**

Crystallisation of the product **9** from methylcyclohexane increases *OY* to 98%. The optical yield of the (*R*)-(+)-ester **11** on crystallisation from a pentane–ether mixture can be raised to 98%. The ester **11** has a configuration which is the opposite of that of the product **10**, whence it follows that, in conformity with Prelog's rule, the CF_3 group should have the same seniority as the methyl group.

In conclusion, one should note that a number of companies have achieved the enzymic synthesis of optically active hydroxyesters. Thus the Kanegafuchi Company produces (*R*)-β-hydroxyisobutyric acid by the microbiological oxidation of n-butyric acid[32] or by the fermentation of isobutyric and methacrylic acids by a strain of *C. rugosa*. The cost of (*S*)-(+)-MHB and (*R*)-(−)-MHB is US $ 2.5 per gram. According to the catalogue of the Aldrich Company, (*R*)-(−)-EHB with $[\alpha]_D = -46°$ (*c* 1, chloroform) is sold at a price of US $ 9 per gram, whilst the price of the racemate is smaller by a factor of 20.[84]

The synthesis of β-hydroxyacids and β-hydroxyesters by the depolymerisation of PHBA and PEHB was examined above in Section III.

V. Synthesis of β-hydroxyesters by the hydrogenation of ketoesters on heterogeneous dissymmetric catalysts

The asymmetrising activity of copper, nickel, and platinum catalysts deposited on crystals of optically active quartz in the asymmetric decomposition of racemic butan-2-ol was first observed by Schwab and coworkers.[85,86] Terent'ev and Klabunovskii[87] extended the studies on catalysts of this type to other reactions. The enantioselectivity of such catalysts was low, the optical yield not exceeding 1%. Akabori and Izumi[3] suggested that palladium bound to the fibroin of natural silk fibres be used as the catalyst for the asymmetric hydrogenation of the C=C bond in the prochiral precursors of amino acids. Its effectiveness was fairly high (for example, $OY = 35.5\%$ in the hydrogenation of azlactone), but there are no literature data on the reproducibility of these results. Nevertheless, the studies carried out have demonstrated the important role of complex formation in asymmetric catalysis and served as a stimulus for the development of dissymmetric metallic catalysts of new types. Among the latter, we may mention the skeletal Raney nickel catalyst and catalysts modified by optically active amino acids or hydroxyacids, which readily form complexes on the surface of the metal. As a result of the modification, centres for enantioselective hydrogenation arise on the surface of the metallic catalysts.

The choice of acetoacetic acid esters [methyl acetoacetate (MAA)[3] and ethyl acetoacetate (EAA)[4]] proved successful. Methods for the preparation of effective catalysts have been developed in relation to these substrates and the characteristic

features of asymmetric hydrogenation have been investigated. Almost 20 years of research were required to increase the OY in this reaction from 10%–15% to 90%–94%.

The achievements in this field have been surveyed in a series of monographs[3,4,87,88] and reviews.[89–93] Factors influencing the enantioselectivity of catalysts for the hydrogenation of β-ketoesters will be examined below and procedures for increasing the optical purity of the hydroxyesters formed will be outlined.

The effectiveness of the modified metallic catalysts‡ depends significantly not only on the stereochemical properties of the modifying agent and the substrate but also on the state of the catalyst surface, its genesis, the nature of the salts used to prepare the initial catalyst mass, the conditions in its reduction, the degree of crystallinity of the catalyst, the size of the crystallites, the nature of their size distribution, and the adsorption and complex-forming capacities of the metallic catalyst in relation to the molecules of the modifying agent and the substrate (product).

According to Balandin's theory of hydrogenation,[94] the effectiveness of the hydrogenation depends significantly on the hydrogen pressure. Since the modification of the catalyst alters its activity usually by diminishing it, the reaction has to be carried out at elevated temperatures and pressures. The complexity of the dependence of OY in the MAA and EAA hydrogenation reactions on the hydrogen pressure (P) has been examined.[95] In the hydrogenation of EAA on Ru–SiO_2–TA, the optical yield OY increases with increase in P, but, after the attainment of a pressure of 7 MPa, it ceases to vary.[96] On the RCo–TA catalyst, the optical yield initially increases with increase in P to 2 MPa and then remains constant up to P = 8 MPa.[97] On RNi–TA, the optical yield is independent of hydrogen pressure in the range 5–10 MPa.[98] When EAA is hydrogenated in the vapour phase on HNi–TA,[99,100] a zero order of the reaction with respect to hydrogen is observed in the pressure range 10–14 MPa (OY = 17.8%).

The enantioselectivity of the hydrogenation of MAA on deposited Ni–SiO_2–TA and Ni–SiO_2–TA–NaBr catalysts depends significantly on the reaction conditions (hydrogen pressure, MAA concentration, nature of the solvent). The experiments have been performed[101] both in the kinetic region (stirring rate 500–800 revolutions per minute), where the rate of reaction and OY are independent of the stirring rate and are proportional to the amount of the catalyst, and in the diffusion region in a rocking autoclave with a MAA : Ni = 8 ratio. When the experiments were carried out in the kinetic region on Ni–SiO_2–TA, the optical yield of the (−)-MHB formed fell from 50% to 30%–35% with increase in hydrogen pressure, while on Ni–SiO_2–TA–NaBr it hardly changed. Evidently, treatment of the catalyst with NaBr imparts to it an increased enantioselectivity and stability. In the diffusion region, OY was 38%–40% and hardly changed as the pressure increased from 1.0 to 8.0 MPa, which agrees with the data of Lipgart et al.[98] An increase in OY when the reaction is carried out in the kinetic region can be achieved by reducing P and by increasing the MAA concentration in EtOAc (Fig. 2). A similar picture is also observed when MeOH and THF are used as the solvent.

It is noteworthy that such effectiveness is attained only at low pressures (0.2–1.0 MPa) and only in the initial stages of the reaction (for degrees of conversion up to 15%). It is not stated in the above communication[101] whether a similar variation is retained at higher conversions. Data concerning the variation of

‡The following notation has been adopted in the literature: RM = skeletal metallic catalyst of the Raney type; M–TA = catalyst modified by (*R*,*R*)-tartaric acid (TA); M–SiO_2–TA = deposited metallic catalyst modified by TA; M–SiO_2–TA–NaBr = catalyst modified by TA with added NaBr; HM = catalyst obtained by reducing the metal oxide in a stream of hydrogen.

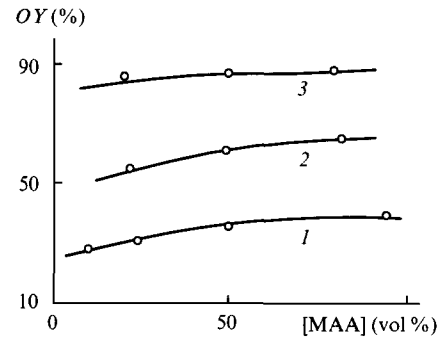


Figure 2. The influence of the MAA concentration in EtOAc on OY in the MAA hydrogenation reaction on the Ni–SiO_2–TA catalyst at pressures of 6.0 MPa (*1*) and 1.0 MPa (*2*) and on the Ni–SiO_2–TA–NaBr catalyst at a pressure of 1.0 MPa (*3*). Degree of conversion 15%.[101]

OY during the reaction are also lacking. Nevertheless the practical value of the proposed methods for increasing the enantioselectivity of the process depends precisely on this factor.

The substrate : catalyst ratio is also important. The maximum optical yield in the hydrogenation of EAA at pressures of 0.1 and 10 MPa has been achieved[98] for the ratio EAA : Ni = 10–20. The independence of OY on the degree of conversion was also noted. This shows that, under the given conditions, the reaction is a kinetically controlled process and the product does not racemise during its occurrence.

In certain cases, OY varied as a function of the degree of conversion and the nature of the solvent simultaneously with the variation of the overall rate of reaction w due to the inhibition of the latter by its product.

The antiparallel variation of OY and w during the reaction has been noted.[95,102] Thus OY decreased with increase in the rate of hydrogenation of MAA on RNi–TA.[102] The optical yield also changed with increase in the degree of conversion:[103] it reached 56.4% for a conversion of 10% and then fell.

According to Balandin's theory of hydrogenation,[94] the product may inhibit the reaction if the adsorption coefficients of the substrate and the product differ greatly. Chernysheva and coworkers[104,105] showed for the first time that the addition of (−)-EHB to a solution of EAA inhibits the enantioselective hydrogenation of the latter on RNi–TA and lowers OY as a result of the preferential adsorption of (−)-EHB on the selective centres. According to the data of Chernysheva and coworkers,[104,105] the ratio of the adsorption coefficients of (−)-EHB and EAA is 3 : 2. As a consequence of this, OY decreases, as can be seen from Fig. 3, where the results of Chernysheva et al.[104] are compared with those of Nitta et al.[106]

The relative adsorption coefficients were calculated[104] by the equation[94]

$$\frac{1}{w} = \frac{b_2/b_1}{kC_2/C_1} + \frac{1}{k},$$

where b_1 and b_2 are the relative adsorption coefficients and C_1 and C_2 are the concentrations of EAA and EHB respectively.

When the reaction is inhibited by the EHB racemate, $b_2 : b_1 = 1 : 2$. It follows from the data of Chernysheva et al.[104] that the degree of adsorption of (−)-EHB on the selective centres exceeds that of (+)-EHB. The introduction into the EAA solution of other strongly adsorbed substances, for example catalyst poisons such as pyridine, thiophene, or amines, exerts a strong inhibiting effect on the enantioselective reaction, the effectiveness of the additives increasing in the sequence (+)-EHB < (−)-EHB < pyridine < thiophene.[104]

For example, the addition of pyridine in the initial stage of the hydrogenation of EAA (for degrees of conversion up to

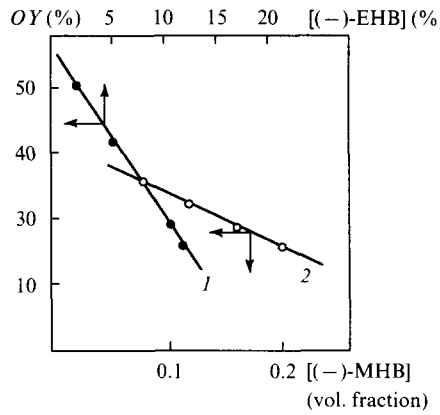


Figure 3. Dependence of OY on the concentrations of the additives in the hydrogenation reactions of EAA on RNi–TA (*1*)[104] and of MAA on Ni–SiO_2–TA (*2*)[106]. The additives are (−)-EHB in the first case and (−)-MHB in the second.

5%–10%) increases OY as a result of the preferential adsorption of this inhibitor on the nonselective centres which were not protected in the modification by the adsorbed TA. Afterwards, as the degree of conversion increases, OY falls almost to zero. In the hydrogenation of EAA on the HNi–TA catalysts, the addition of pyridine and butylamine increases OY in the initial stage of the reaction from 11% to 17% and 50% respectively.[99] After the introduction of pyridine or thiophene, the optical yield for y = 10% increased from 7% to 12% and from 2.5% to 11.5% respectively.[105] Chernysheva and coworkers[104,105] determined the optical yields polarimetrically, taking into account the change in the specific rotation of EHB for low degrees of conversion ($y \leqslant 7\%$):

$$\lg[\alpha]_D = 1.55 - 0.2 \lg y .$$

A significant increase in OY in the hydrogenation of MAA[101] was achieved by adding unsaturated compounds, which are hydrogenated preferentially on nonselective centres. The fraction of enantioselective centres on which MAA is hydrogenated increases under these conditions (Fig. 4).

The addition of benzene, which is not hydrogenated under these conditions, also ensures an appreciable increase in OY.

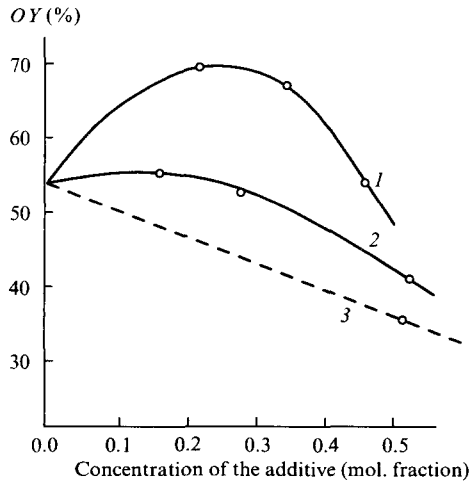


Figure 4. The influence of added benzene (*1*), cyclohexene (*2*), and ethyl acetate (*3*) on the optical yield of (−)-MHB in the hydrogenation of MAA on Ni–SiO_2–TA (pressure 1.0 MPa, degree of conversion 15%).[101]

However, its use as a solvent in the hydrogenation of MAA lowers OY, apparently as a result of the displacement of TA from the modified centres of nickel.

A complex pattern in the variation of OY in the hydrogenation of MAA on RNi–TA catalysts prepared by different procedures (the 1 : 1 Ni–Al alloy was leached with a 20% NaOH solution at different temperatures in the range 278–353 K) has been noted.[103] When the reaction was carried out on the most active catalyst, a flat maximum (OY = 18%) was observed on the curve relating OY to the degree of conversion at y = 70%, whereas in the case where less active catalysts were employed the maximum optical yield (45%–50%) was attained at y = 25%.

Table 5. Chemical and phase composition of the RNi–TA catalysts.[105]

Composition (%)	Alloy specimen			Catalyst specimen	
	1	2	3	2	3
Chemical					
Ni	50.0	45.2	38.3	79.1	91.4
Al	50.0	51.2	59.7	17.7	8.5
Cr	–	3.6[a]	2.0[a]	1.0	0.10
Ti	–	–	–	2.1	0.03
Phase					
$NiAl_3$	–	25.1	51.2		
Ni_2Al_3	90.0	74.9	48.8		
Bayerite				3.0	2.1
Ni				91.5	97.9
Al				5.4	0.0

[a] Cr + Ti.

The variation of OY with y is influenced by the chemical and phase compositions of the initial Ni–Al alloys (Table 5).[105] A decrease in the nickel content, i.e. an increase in the content of the intermetallic compound $NiAl_3$ in the alloy, promotes a more complete removal of aluminium in the leaching of the alloy (cf. the catalyst specimens *1*–*3* in Fig. 5), which should apparently increase OY in the hydrogenation of EAA for low degrees of conversion (y = 10%–30%). However, as can be seen from Fig. 5, the dependence of OY on y is complex and for this reason comparison of the enantioselectivities of different catalysts only for low degrees of conversion, as was done,

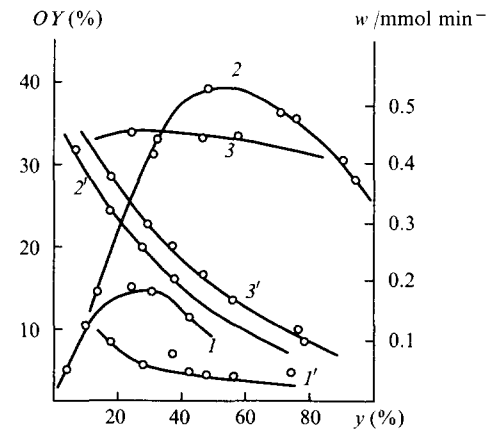


Figure 5. Dependence of the optical yield OY (*1*, *2*, *3*) and of the rate of hydrogenation of EAA w (*1′*, *2′*, *3′*) on the degree of conversion y on specimens of the RNi–TA catalyst obtained from alloys with different initial compositions[105] (Table 4):
(*1*, *1′*) specimen 1; (*2*, *2′*) specimen 2; (*3*, *3′*) specimen 3.

for example, by Nitta et al.,[101] is clearly inadequate: it is necessary to follow the variation of OY over the entire range of y.

The nature of the dependence of OY on y is also influenced by the strength of the bond between hydrogen and the catalyst surface. Catalysts obtained from $NiAl_3$ are known to contain a greater amount of weakly bound hydrogen than catalysts prepared from alloys in which the intermetallic compound Ni_2Al_3 predominates (specimen *3*).[104,105] A higher optical yield is attained on the latter.

Another way of increasing OY is by controlling the degree of dispersion of the catalyst metal on the carrier surface. As was shown for the first time by Klabunovskii and coworkers,[4,107] the quantity OY in the hydrogenation of EAA on the $Ru-SiO_2-TA$ catalysts depends significantly on the degree of crystallinity of ruthenium. The optical yield increases with increase in the catalyst reduction time and attains its maximum value for an average size of the crystallites of 4.5 nm. On the catalyst with 8.0 nm crystallites, the enantioselectivity of the hydrogenation reaction diminishes (Fig. 6).

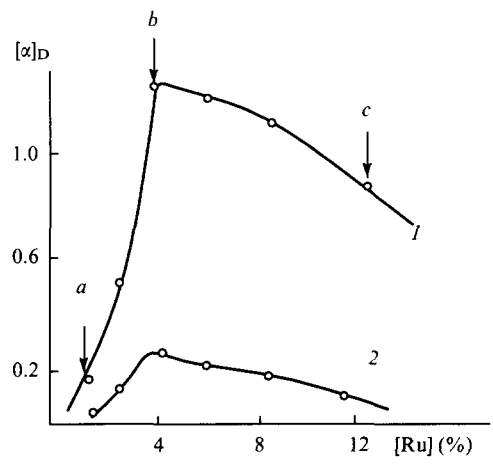


Figure 6. The influence of the metal content in the $Ru-SiO_2-TA$ catalyst on its asymmetrising capacity — on $[\alpha]_D$ for the product — in the EAA hydrogenation reaction. The preliminary catalyst reduction times were 0.5 h (*1*) and 5 h (*2*). Points *a*, *b*, and *c* on curve *1* correspond to ruthenium crystallite sizes of 1.6, 4.5, and 8.0 nm respectively.[4]

The important role of the size of the crystallites and of their size distribution was confirmed in a study of the enantioselective hydrogenation of MAA on the $Ni-SiO_2-TA$ catalyst.[108] By varying the conditions in the preparation of the catalyst, it was possible to achieve a narrow peak in the size distribution of nickel crystallites on the surface. Ni–TA catalysts (without a carrier) of different composition were investigated:[109] nickel boride (Ni–B), nickel phosphide (Ni–P), Raney nickel (RNi), and nickel black obtained by the decomposition of nickel formate (DNi) or by the reduction of NiO (HNi). The HNi–TA ($OY = 56.2\%$), DNi–TA (42.3%), and RNi–TA (26.7%) catalysts exhibited the highest enantioselectivity. On the Ni–B and Ni–P catalysts, the optical yield did not exceed 3%–5%. Their low enantioselectivity was attributed to the cryptocrystallinity of the Ni phase (it is X-ray amorphous) and also to the strong adsorption of TA.[110] After the modification of the Ni–B catalyst by tartaric acid, the latter was adsorbed in an amount of 4.9×10^{-3} mmol g^{-1}, which is 9 times greater than on RNi. Careful washing of the Ni–B–TA catalyst and its treatment with a solution of alkali led to the removal of boron from the surface and to a decrease in the TA content on the surface to 0.5×10^{-3} mmol g^{-1}. As a result, the optical yield in the hydrogenation of MAA increased to 26.7%, while the Ni–B–TA catalyst was virtually converted into HNi–TA as a result of the liberation of part of the surface. According to the data of Nitta et al.,[109] the adsorption of tartaric acid on the catalyst surface in an amount exceeding that required for the specific modification of the surface does not influence significantly the enantioselectivity. This conclusion conflicts with data[99,100] indicating a linear increase in OY with increase in the fraction of the TA dianion on the DNi surface.

The increase in the size of the nickel crystallites from 6 to 20 nm increases OY from 36.1% to 54.9%.[111] This can be accounted for with the aid of a stereochemical model of the catalytically active centre,[4] according to which the accommodation of the catalytic complex on the surface of the enantioselective catalyst requires fairly large crystalline formations (faces, planes). This view is confirmed also by data[110] according to which the reduction of NiO leads to the formation of cryptocrystalline, almost amorphous, nickel, which does not exhibit enantioselectivity after modification.

The high effectiveness of the coarsely crystalline TNi–TA specimens[109] is attributed to the presence in this catalyst of impurities remaining after the decomposition of the formate. These data also agree with the previously proposed model[4] and confirm the influence of the crystallinity of the metal on its enantioselectivity. Since cryptocrystalline nickel catalysts are ineffective in asymmetric hydrogenation, in order to increase the enantioselectivity of the MAA hydrogenation reaction it is desirable to produce a catalyst with relatively large crystallites having uniform dimensions.[108,110–115]

It had been noted earlier[4] that aluminium oxide is relatively unsuitable as a carrier for asymmetric hydrogenation. Thus the $Ru-Al_2O_3-TA$ catalyst did not exhibit enantioselectivity in the hydrogenation of EAA, whereas $Ru-SiO_2-TA$ had a weak activity. This can be explained by the fact that ruthenium interacts much more strongly with Al_2O_3 than with SiO_2. However, by varying the conditions in the formation of the catalyst, it was also possible to obtain enantioselective catalytic systems when Al_2O_3 was used as the carrier, for example $Ni-Al_2O_3-TA$ and $Ni-Co-Al_2O_3-TA$ with a metal content of 20%.[116] These catalysts were reduced at 773 K and EAA was hydrogenated at 393–408 K and a pressure of 10–12 MPa. The optical yield on the first catalyst was 76.0% and that on the second was 62.6%. Such relatively high values of OY can be due to the presence on the nickel surface of incompletely reduced residues of the metal salts, which decrease the fraction of the small crystallites. The reduction of the catalyst under mild conditions (for example at a reduced partial pressure of hydrogen) increases the ratio of large crystallites and their enantioselectivity.

The formation of small nickel crystallites can be prevented by introducing into the catalyst mass (nickel and aluminium hydroxides), before its deposition, a certain number of Fe^{3+} ions, which weaken the interaction between nickel and the carrier.[117] Thus the introduction of up to 10% of Fe^{3+} increases the enantioselectivity of the $Ni-Al_2O_3-TA$ catalyst in the hydrogenation of MAA, increasing OY from 18% to 38%, i.e. making the effectiveness of the catalyst comparable to that of $Ni-SiO_2-TA$. On the other hand, the addition of Fe^{3+} in the preparation of $Ni-SiO_2$ lowers both the optical and the chemical yields of the MAA hydrogenation product (Fig. 7). The introduction of a palladium salt has a similar effect.[111] It is noteworthy that the promoting effect of Fe^{3+} is manifested only when Al_2O_3 is used as the carrier: in this case, the increase in the Fe : (Fe + Ni) ratio to 10% increases OY from 16% to 38%, whereas the addition of iron in the preparation of the $Ni-SiO_2-TA$ catalyst lowers OY from 30% to 10%.[117]

The use of a mixed carrier instead of silica gel (the $Ni-Al_2O_3-SiO_2-TA$ catalyst) lowers OY from 49.7% to 18.3%, although the size of the crystallites increases under these conditions from 8 to 24 nm. One should note in this connection that the nickel catalyst on a zeolite (1 : 5), obtained by impregnation, is less effective in the hydrogenation of MAA. The optical yield attained on this catalyst is 7.3%, whereas on the

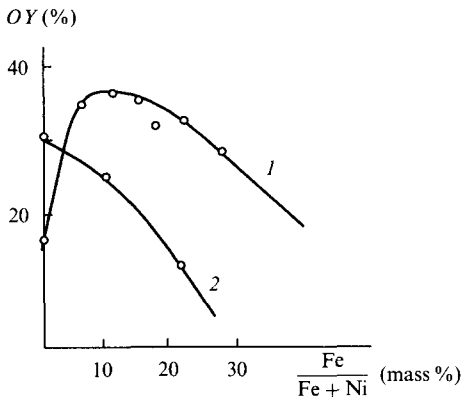


Figure 7. Dependence of OY in the MAA hydrogenation reaction on the iron content in the Ni–Fe–Al_2O_3–TA (*1*) and Ni–Fe–SiO_2–TA (*2*) catalysts.[117]

Ni–zeolite–TA catalyst, obtained by joint deposition, OY = 45.6%.[108]

In order to investigate the role of the size of the crystallites at a constant surface coverage,[118] the $Ni_3(OH)_4Si_2O_5$ system was prepared on the basis of chrysotile — a layered silicate.[119] Its reduction in a stream of hydrogen afforded the 59.4% Ni–SiO_2 catalyst with a constant degree of surface coverage and a uniform dispersity, which could be regulated by varying the reduction conditions. An increase in the temperature of the reduction of Ni-chrysotile helped to increase the size of the crystallites ($\bar{D}$) and in the temperature range 673–973 K $\bar{D}$ varied from 4 to 11 nm, while OY in the hydrogenation of MAA reached 40% (Fig. 8). The nature of the initial nickel salt, used in the preparation of Ni-chrysotile, influenced significantly the size of the crystallites and OY.[120]

Vedenyapin et al.[121] investigated the influence of platinum metals, introduced into various metallic catalysts, on the enantioselectivity of the latter. The TA-modified palladium catalyst did not exhibit an activity in the enantioselective hydrogenation of EAA. The introduction of even 5% of palladium into the RCu–TA catalyst, capable of promoting enantioselective hydrogenation albeit with a low effectiveness, led to a decrease in OY from 9% to 1%.[121]

The 10% (Ni–Pd)–aerosil and 10% (Ni–Pd)–Al_2O_3 catalysts were obtained by impregnating the carriers with solutions of the appropriate salts.[122] The catalysts were dried and reduced at 630 K in a H_2–He stream. Catalysts of another series were prepared by impregnating Ni–SiO_2 with a $PdCl_2$ solution. The modification was carried out with a 5% TA solution at pH 5. Similar results in the hydrogenation of EAA were obtained on the catalysts of both series: the optical yield was 7%–9% for an overall rate of reaction of 0.1 mmol min^{-1} (g catalyst)$^{-1}$.

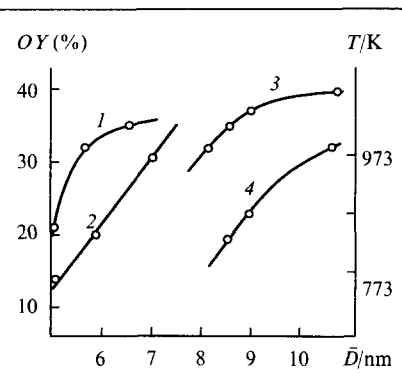


Figure 8. Dependence of the enantioselectivity of the Ni–SiO_2–TA catalyst, obtained from Ni-chrysotile, in the MAA hydrogenation reaction (333 K, 10 MPa) on the average size of the crystallites ($\bar{D}$) (*1*, *3*) and the influence of the temperature of the reduction of the catalysts on $\bar{D}$ (*2*, *4*): (*1*, *2*) initial salt $Ni(NO_3)_2 \cdot 6H_2O$; (*3*, *4*) initial salt $NiCl_2 \cdot 6H_2O$ (according to the data of Nitta and coworkers[119, 120]).

The modification of the RNi–Ru catalyst obtained by leaching ternary Ni–Ru–Al alloys containing 70% of aluminium was achieved by employing a 2% solution of TA at pH 4.5.[123] With increase in the ruthenium content, OY decreased. According to the data of Vedenyapin et al.,[123] the introduction of palladium or ruthenium as additives into nickel or copper catalysts does not promote the enantioselective hydrogenation of EAA. A similar picture was observed when the DNi–TA catalyst, obtained by decomposing nickel formate, was employed.[110] The addition of 15% of palladium lowered the optical yield in the MAA hydrogenation reaction from 50% to zero. After the introduction of palladium, the amount of TA adsorbed by the catalyst during its modification diminished from 0.01 to 0.001 mmol (g Ni)$^{-1}$ as a consequence of the displacement of TA from the surface by palladium. Thus, in conformity with the data of Nitta et al.,[111] the high effectiveness of nickel catalysts alloyed with 1% of platinum metals, observed by Orito and coworkers,[124–128] can be accounted for by the influence of these additives on the formation of the catalyst surface and primarily on the crystallinity of nickel.

Orito and coworkers[124–128] showed that the 1:1 nickel catalyst on kieselguhr (Kg), alloyed with 1% of noble metals and modified with (*R*,*R*)-TA, exhibits an exceptionally high enantioselectivity in the hydrogenation of MAA to MHB. The optical yield of MHB reached[127] 99.4% on the Ni–Pd–Kg catalyst. However, Orito and coworkers[124–128] determined the values of OY polarimetrically and adopted $[\alpha]_D = +20.9°$ for the optically pure MHB. Since it was later established[46] that the specific rotation of MHB is 22.95° and not 20.9°, the highest values of OY in the above investigations should have been 79.0%–90.5%, which are also extremely high parameters. The importance of the results obtained led us to describe here the methods for the preparation of the catalyst and for carrying out experiments on the hydrogenation of MAA.[124]

Kieselguhr [manufactured by the National Chemical Laboratory for Industry (Japan)] was introduced, without additional purification,§ into a solution of nickel nitrate and a platinum metal salt in an amount such that the ratios Ni : Pt : Kg = 100 : 1 : 100 were attained. The mixture was allowed to stand for 1 h and was then treated with a solution of sodium carbonate. The precipitate was thoroughly washed and dried for 24 h at 383 K. The 3 g catalyst specimen was heated by a quartz lamp in a stream of H_2 (7 dm^3 h^{-1}) up to 573 K for 1 h, after which it was cooled and added to a 100 ml of a 1.5% aqueous solution of (*R*,*R*)-TA at pH 4.1 bubbled with nitrogen, reducing the temperature of the solution gradually to 358 K. The catalyst was then centrifuged and washed initially twice with water (with 25 ml in each case) and then with methanol and the solvent in which the hydrogenation was to be carried out. The reaction was performed in an autoclave with stirring at a pressure of 6–8 MPa and with a substrate : catalyst ≈ 14 : 1 ratio. The reaction temperature was raised from 293 K to the specified level at a rate of 0.7 K min^{-1}. When the absorption of hydrogen was completed, the catalyst was filtered off and the product distilled.

The compilation in Table 6 presents the maximum optical yields of MHB under different conditions.¶ By carrying out the reaction in THF and by adding small amounts of carboxylic

§Personal communication by Prof. Orito.

¶ The optical yields obtained by Orito and coworkers[124–128] and presented in Table 6 were corrected in accordance with the new value of the specific rotation of MHB $[\alpha]_D = 22.95°$.

Table 6. Enantioselective hydrogenation of MAA on deposited nickel catalysts alloyed with added platinum metals and modified by (*R,R*)-tartaric acid (according to the data of Orito and coworkers [124-128]).

Number of experiment	Catalyst	Solvent	w /mmol h^{-1} (g catalyst)$^{-1}$ [a]	$[\alpha]_D^{20}$	OY(%)
1 [b]	Ni–Kg	without solvent	5.9	12.20	53.2
2	Ni–Rh–Kg	"	7.8	13.75	59.9
3	Ni–Pt–Kg	"	9.7	14.20	61.9
4 [c]	Ni–Pt–Kg	THF	4.7	15.00	65.4
5 [d]	Ni–Pt–Kg	THF	7.2	18.05	78.6
6 [e]	Ni–Pd	without solvent	3.8	9.15	39.8
7	Ni–Pd–Kg	"	8.7	14.65	63.8
8 [d]	Ni–Pd–Kg	THF	6.9	18.22	79.4
9 [d]	Ni–Pd–Kg	THF	2.8	20.10	87.6
10 [d]	Ni–Pd–Kg	THF	2.5	20.44	89.1
11 [f]	Ni–Pd–Kg	THF	2.5	20.79	90.6
12 [g]	Ni–Pd–Kg	THF	2.6	20.49	89.3
13	Ni–Pd–C	without solvent	5.6	13.02	56.7
14	Ni–Pd–Al_2O_3	"	5.2	11.13	48.5
15	Ni–Ir–Kg	THF	4.9	16.50	71.9
16 [c]	Ni–Ru–Kg	without solvent	8.8	11.35	49.5
17	Ni–Ru–Kg	"	7.8	12.35	53.8
18 [h]	Ni–Ru–Kg	"	9.3	12.05	52.5
19 [d]	Ni–Ru–Kg	THF	6.7	16.75	73.0
20 [i]	Ni–Ru	without solvent	1.6	4.1	17.0

Note. Composition of catalyst: nickel : platinum metal : kieselguhr = 100 : 1 : 100. Samples: 2.3 g of catalyst, 2.3 g of MAA, and 44 ml of the solvent. Catalyst modification conditions: 1.5% aqueous TA solution, pH 4.3, 357 K. Hydrogenation conditions: pressure 5.5 MPa, temperature 294–403 K.

[a] Rate of formation of the (R)-(−)-MHB enantiomer. [b] Catalyst composition Ni : Kg = 1 : 1. [c] The catalyst was modified at 293 K. [d] 1 ml of AcOH was added. [e] Catalyst composition Ni : Pd = 100 : 1. [f] 0.05 g of HCOOH was added. [g] 0.5 g of benzoic acid was added. [h] Catalyst composition Ni : Ru : Kg = 100 : 3 : 100. [i] Catalyst composition Ni : Ru = 100 : 1. Modification conditions: pH 4.5, 293 K. Samples: 0.2 g of the catalyst, 41 ml of EAA. The hydrogenation was carried out at 333 K (according to the data of Klabunovskii and Vedenyapin [4]).

acids into the reaction mixture, the OY for the product is increased by 6%–10%.

The method of synthesis of MHB with OY up to 90.6%, in which the modification with tartaric acid is carried out at pH 4.3–4.5 (0.68–0.72 g of NaOH on 1.5 g of TA) at 357 K, was developed for the Ni–Pd–Kg catalyst. Before the reaction, the catalyst (2.3 g sample) must be heated for 4 h in THF without stirring, having added 1.5% of acetic acid, at 382 K and a pressure of 5.5 MPa (experiment No. 10). The reaction mixture (MAA in 44 ml of THF to which 1 ml of AcOH has been added) is kept initially without stirring for 1 h at the same temperature and pressure and is then stirred for 10–20 h. The optical yield of the MHB thus obtained reaches a maximum value of 90.6% (experiment No. 11). Instead of acetic acid, formic or benzoic acid may be added. The optical yield of the product increases if the added monocarboxylic acid has a pK_1 lower than that of the modifying agent — tartaric acid ($pK_1 = 2.89$).

It follows from Table 6 that the alloying of the nickel catalyst with platinum metals increases significantly the enantioselectivity and the overall rate of the reaction. The deposited Ni–Ru–Kg catalyst is more effective ($OY = 50\%$) than the Raney RNi–Ru catalyst without a carrier, on which OY is 4% and 17% respectively in the MAA and EAA hydrogenation reactions.[4]

An increase in the temperature of the modifying TA solution from 293 to 353–363 K helps to increase the optical yield of MHB. When the reaction is carried out in alcohols, OY diminishes but the overall rate of reaction increases. The best solvent has proved to be THF and ethyl acetate with added acids (acetic, formic, or benzoic). The antiparallel variation of OY and the overall rate of reaction, observed earlier by Orito and coworkers,[124-128] was confirmed.[4] Among the carriers investigated (activated charcoal, aluminium oxide, silica gel, kieselguhr), best results were obtained with kieselguhr.

Unfortunately there are no literature data on the reproducibility of the results of the studies by Orito and coworkers.[124-128] Nevertheless, a question arises concerning the reason for the high enantioselectivity of nickel catalysts alloyed with other metals and especially concerning the role of kieselguhr as the carrier. Bimetallic catalysts based on nickel and copper with added platinum metals (ruthenium and palladium) did not exhibit an appreciable enantioselectivity in the EAA hydrogenation reaction.[4,123]

Nitta et al.[111] investigated in detail modified nickel catalysts on carriers, including kieselguhr. They exhibited a high enantioselectivity, but kieselguhr as a carrier had no special properties. Apparently the addition of platinum or palladium at the nickel catalyst preparation stage promotes a more complete reduction of nickel and the formation at nickel crystallites of optimum size.[111] The NiO reduction process is influenced significantly by Cl^- and Br^- anions. The addition of $PdCl_2$ to the initial $NiO–SiO_2$ system promotes the reduction of NiO but has little influence on the enantioselectivity.[111]

Contrary to the data of Orito and coworkers,[124-128] the deposition of nickel on kieselguhr of the Shimalite brand or on Al_2O_3 with subsequent modification by (*R,R*)-tartaric acid did not make it possible to attain a value of OY in the MAA hydrogenation reaction in excess of 54–68% even in the presence of a high metal content on the carrier.[129] Similar optical yields were also obtained when nickel was deposited on TiO_2 (70%) and ZrO_2 (68%). The reactions were carried out at a pressure of 9 MPa and a temperature of 393 K.[129]

The higher values of OY attained by Orito and coworkers[124-128] can apparently be partly accounted for by the high nickel content on the carrier (50%), which actually converts the deposited catalyst into nickel black, and also by the specially favourable conditions in the formation of the catalyst created by the addition of platinum metals. It is also possible

Table 7. Conditions in the preparation of the Ni–SiO_2–TA catalysts for the hydrogenation of MAA (Ni : SiO_2 = 1 : 1).

Conditions	Methods adopted by Nitta et al.[111]			Method adopted by Orito et al.[124]
	A	B	C	
$Ni(NO_3)_2 : Na_2CO_3$	1	1.2	0.83	1
Deposition temperature / K	348	358	273	298
Ageing time / min	15	30	5	60
Drying temperature / K	383	393	323	383
Drying time / h	24	45	20	24
$NiCO_3$ content in deposit (%)	35–40	7–10[a]	60–65	–

[a] $Ni(OH)_2$ content.

that the kieselguhr employed in the above studies contained promoting admixtures.

Nitta et al.[111] concluded that the high effectiveness of the nickel catalysts under discussion[124–128] may be accounted for by the special conditions in their formation. According to Nitta et al.,[111] the introduction of 1% of palladium into the Ni–SiO_2 catalyst in the stage involving the reduction of the $NiCO_3$–SiO_2 system promotes the reduction of the salt, a decrease in the process temperature, and the formation of larger nickel crystallites. Nitta et al.[111] attempted to reproduce the data of Orito and coworkers.[124–128] The Ni–SiO_2 catalytic systems were prepared by three methods differing in the conditions in the deposition of the catalyst and its reduction. The influence of the introduction of palladium into the catalysts on the formation and enantioselectivity of the catalysts and the role of kieselguhr as the carrier were also investigated.

Table 7 presents the conditions for the preparation of the nickel catalysts described by Nitta et al.[111] and for comparison the conditions quoted by Orito et al.[124] Nitta et al.[111] used silica gel (60–200 mesh) with a specific surface of 600 $m^2 g^{-1}$ and kieselguhr with a specific surface of 5.7 $m^2 g^{-1}$ supplied by the Yoneyama Yakuhin Company. The suspension of the carrier was impregnated with a solution of nickel nitrate and precipitated with a solution of sodium carbonate at 348 K. After drying (383 K), the catalysts were reduced in a stream of hydrogen for 1 h at 773 K. In order to obtain the Ni–Pd–SiO_2 system, $PdCl_2$ was added to the catalyst mass before its reduction (Ni : Pd : carrier = 100 : 1 : 100).[111] As can be seen from Table 7, methods A, B, and C differ in the severity of the conditions during the deposition and treatment of the catalyst mass. The catalyst obtained by method C contained an excess of $NiCO_3$. Method A is distinguished by milder conditions, similar to those adopted by Orito and coworkers.[124–128] Method B affords a deposit containing less effectively reducible $Ni(OH)_2$, the reduction of which even in the presence of palladium gives rise to larger crystallites.[115] Depending on the composition of the initial mixture, the catalysts differ significantly in their enantioselectivity in the MAA hydrogenation reaction in EtOAc at 333 K and a pressure of 1 MPa. It was shown[111] that nickel catalysts with added palladium, deposited on silica gel or kieselguhr, are usually less effective than the catalysts without such an additive, which conflicts with the data of Orito et al.[124] Admittedly, the introduction of palladium into the catalyst obtained by method A promoted some increase in enantioselectivity as a consequence of the increase in the average size of the nickel crystallites (Table 8).

The use of kieselguhr did not increase but actually somewhat diminished OY even when the modification was carried out by the method of Orito et al.[124] at pH 4.1. The reaction rates on all the Ni–SiO_2–TA catalysts were similar and amounted to 0.4–0.8 mmol min^{-1} (g Ni)$^{-1}$. The introduction of palladium decreased somewhat the average size of the crystallites, which increased the rate of reaction but did not increase OY, whereas, according to the data of Orito et al.,[124] the catalysts on kieselguhr with added palladium are more active [the rate of reaction is 2.5–8.7 mmol min^{-1} (g Ni)$^{-1}$] and enantioselective (OY = 63.8%–89.1%). Thus, contrary to the data of Orito and coworkers,[124–128] the introduction of palladium and the use of kieselguhr as the carrier did not lead to the formation of specially effective catalysts.[111]

Table 8. The influence of the method of preparation of the catalyst, the nature of the carrier, the reduction temperature (T_r), and added palladium on the enantioselectivity of the catalysts for the hydrogenation of MAA to (−)-MHB (according to the data of Nitta et al.[111]).

Method of preparation[a]	Catalyst[b]	T_r / K	$\bar{D}$ / nm	OY (%)
A	Ni–Kg	523	31	32.5
A	Ni–Pd–Kg	523	16	26.3
A	Ni–Kg[c]	573	31	12.1
A	Ni–SiO_2	573	–	23.8
		673	9	50.6
A	Ni–Pd–SiO_2	573	–	27.8
		673	12	41.6
B	Ni–SiO_2	673	4	29.8
B	Ni–Pd–SiO_2	673	5	20.1
C	Ni–SiO_2	573	13	43.4
C	Ni–Pd–SiO_2	573	13	30.1
C	Ni–SiO_2[c]	573	13	36.8
C	Ni–Pd–SiO_2[c]	573	13	34.6
C	Ni–Pd–Kg	573	12	27.7
	Ni–Pd–Kg[c]	573	–	63.8[d]
	Ni–Pd–Kg	573	–	89.1[e]

[a] See Table 7. [b] Ni : Pd : carrier = 100 : 1 : 100; modification by (*R*,*R*)-tartaric acid at pH 5.1. [c] Modification carried out at pH 4.1. [d] Experiment No. 7 in Table 6. [e] Experiment No. 10 in Table 6.

With increase in the fraction of $NiCO_3$ in the catalyst mass above 25% there is an increase in the specific surface and in the average size of the nickel crystallites (from 5 to 18 nm). OY passes through a maximum corresponding to the catalyst obtained from the catalyst mass containing 37% of $NiCO_3$ and reduced at 773 K. The increase in the fraction of $NiCO_3$ to 58% makes it possible to lower the reduction temperature to 573 K. This leads to an increase in $\bar{D}$ to 15 nm, which promotes an increase in OY. Hence it follows that the enantioselective hydrogenation is a structure-sensitive reaction and may be used as a method for the monitoring of the size distribution of the nickel crystallites. Fig. 9 presents the variations of the catalytic activity and the optical yield in the MAA hydrogenation reaction on Ni–SiO_2 with the fraction of $NiCO_3$ in the catalyst mass. The size of the nickel crystallites is related, in its turn, to this quantity.

Studies have shown[114,115] that the formation of the catalyst is greatly influenced by the additives, the nature of the initial salts, and the reduction conditions. The high effectiveness of the bimetallic catalysts deposited on kieselguhr may therefore be

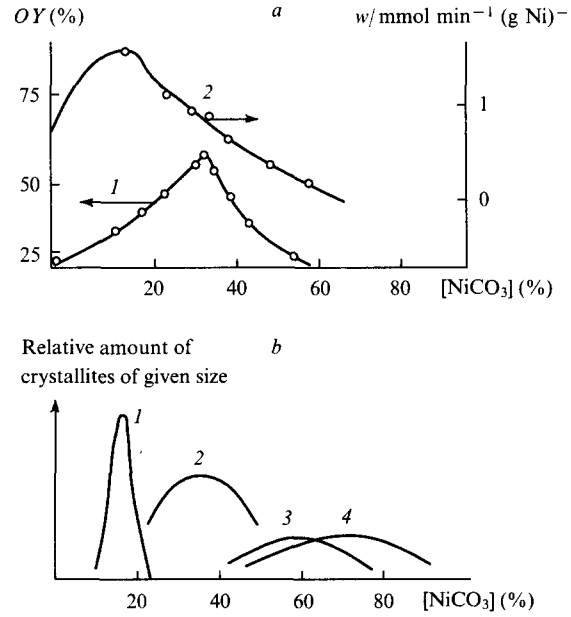


Figure 9. The influence of the $NiCO_3$ content in the initial catalyst mass (catalyst reduction temperature 673 K) on the optical yield of MHB (*1*) and the catalytic activity (w) of Ni–SiO_2–TA (*2*) in the MAA hydrogenation reaction (*a*) and also on the average size of the nickel crystallites (*b*). Curves *1–4* (*b*) correspond to $\bar{D}$ = 3.5, 8.0, 16.0, and 18.0 nm respectively (according to the data of Nitta et al.[114,115]).

caused by the precise influence of these factors on the formation of the structure of the catalyst surfaces and primarily on the size of the nickel crystallites.[106,108,109,113–115]

The introduction of palladium into the catalyst apparently affects the degree of reduction of nickel, which occurs in this case at lower temperatures. This influence depends greatly on the nature of the initial salts: the presence of palladium promotes the reduction of $NiCO_3$, formed on precipitation with sodium carbonate, but has little effect on the reduction of $Ni(OH)_2$. The presence of the carrier accelerates the conversion of part of $NiCO_3$ into $Ni(OH)_2$, but the reduction of the hydroxide requires more severe conditions.

As already mentioned,[124–128] the addition of AcOH increases significantly OY in the hydrogenation of MAA on Ni–Pd–Kg. The addition of certain salts into the modifying TA solution also helps to increase OY, the nature of the anion playing an important role. NaBr proved to be the most effective modifying additive to RNi–TA.[46]

High concentrations of halide salts in the modifying TA solution have a negative effect on the rate of reaction and on OY,[118] but the addition of NaI (or KI) at very low concentrations tends to increase the optical yield. It has been found that NaI reduces OY sharply at a concentration of just 0.002%, whereas NaBr is effective even at concentrations higher by a factor of 100. This is associated with the fact that the iodide is adsorbed on nickel much more strongly than the bromide. Thus the anion affects OY no less strongly than the cation.[46]

The nature of the cation is important in the leaching of the Ni–Al alloy and in the establishment of a suitable pH of the modifying tartaric acid solution. Best results were achieved when Na^+ ions were employed: at a NaBr concentration of 8% and a TA concentration of 1%, the optical yield in the hydrogenation of MAA was 70.2%. Li^+ and Rb^+ ions hardly affect OY. The cations are coordinated to the oxygen in TA and MAA adsorbed on nickel, sodium and potassium participating in the octahedral coordination, which intensifies the template effect in the stereochemical interaction of TA with MAA (and MHB). The anions are by themselves incapable of showing the template effect, particularly at high salt concentrations, their function consisting in fixing the appropriate amounts of the cation on the catalyst surface, needed for coordination to the TA–MAA (MHB) complex. The influence of NaBr is also manifested by the fact that the salt is a weak poison for the nickel catalysts. It blocks the most active centres on the nickel surface, intensifying thereby the enantioselective effect of the modified centres.

According to Nitta et al.,[111] the introduction of chlorides or bromides into the catalyst mass during the formation of deposited catalysts promotes an increase in OY by virtue of the increase in $\bar{D}$, but the overall rate of reaction decreases under these conditions. The addition of the salts $NiCl_2$, NaCl, $FeCl_2$, and NaBr or of the acids HCl or HBr to the catalyst mass prepared by method A increases OY from 36.1% to 49.7%–57.5%. With increase in $\bar{D}$ (from 13 to 20–30 nm), a narrower size distribution of the nickel crystallites is obtained.[111]

The increase in OY after the addition of $NiCl_2$ is of interest. The introduction of 29.8% of this salt into the catalyst mass, prepared by methods A, B, or C, diminishes sharply the specific surface of the reduced nickel (the reduction was carried out at 623 K for 1 h), which indicates an increase in $\bar{D}$. Depending on the method employed, OY increases from 36.1% to 54.9% (A), from 19.3% to 51.0% (B), and from 39.4% to 53.2% (C) respectively. The sharp diminution in the specific surface indicates not only the growth of $\bar{D}$ but also the presence on the surface of chloride residues, which hinder the adsorption of hydrogen. At the same time, the Cl^- ions remaining on the catalyst after its reduction may act as a promoting additive, i.e. may behave similarly to NaBr in the modifying solution.[46]

The RNi–TA–NaBr catalyst was obtained by leaching the 42:58 Na–Al alloy at 373 K.[46] The catalyst was washed 15 times with portions of deionised water and was modified in 1% (*R*,*R*)-TA solution containing 10 g of NaBr at 373 K in the course of 1 h. After the modification, the catalyst was again washed with water and methanol. MAA was hydrogenated in an EtCOOMe + 0.2 ml AcOH solution at a pressure of 9 MPa and a temperature of 373 K. The rate of reaction was 0.2 mmol min^{-1} (g Ni)$^{-1}$. A threefold repetition of the modification procedure increased OY from 83.1% to 88.6%. Under the same conditions but without the addition of NaBr and AcOH, OY was 31.2%. The introduction of NaBr at a concentration of 0.01–0.04 mmol (g Ni)$^{-1}$ did not affect the degree of adsorption of TA on nickel and the optical yield increased in proportion to the NaBr concentration. This has been attributed[46] to the presence on the surface of the modified catalyst of two types of centres:[4] selective centres, modified by TA, on which the (–)-enantiomer is formed, and nonselective centres on which the MHB racemate is produced.

This method also has its negative aspects: as stated above, NaBr diminishes the activity of the nonselective centres and lowers the overall rate of reaction. In order to compensate for this negative effect, it is necessary to increase the reaction pressure and temperature and this entails a decrease in regioselectivity and the appearance of side products, in particular the ester $MeCH(CH_2COOMe)OCOCH_2CH(OH)Me$. The behaviour of the deposited nickel catalyst is somewhat different from that of the Raney catalysts. The presence of residual amounts of Cl^- ions in the Ni–SiO_2 catalyst imparts stability to the latter in repeated hydrogenation. On the other hand, the Ni–SiO_2 (1:1) catalyst modified by TA with added NaBr is not quite so effective[111] as RNi.[46] The modification by NaBr increases OY in the MAA hydrogenation reaction from 36.1% to 46.0%, but, after repeated hydrogenation on the same portion of the catalyst, OY fell to 11.0%, while the catalyst promoted by the addition of $NiCl_2$ to the catalyst mass before reduction retained its stability in three consecutive experiments (y = 90%, 79%, and 81% for OY = 52.7%, 55.0%, and 54.9% respectively). This can be explained not only by the presence of

residual amounts of the halogen on the nickel surface but also by a more uniform size distribution of the nickel crystallites. Promotion by halides (nickel chloride) of the initial catalyst mass increases the degree of reduction of NiO to the metal.[111] This effect is manifested to a particularly notable extent in the reduction of the catalyst mass obtained by method B and containing $Ni(OH)_2$, which is reduced with difficulty as a consequence of the strong interaction with the carrier.[117] As a result of this, the catalyst obtained has a higher activity but a lower enantioselectivity.

The low enantioselectivity of the $Ni-Al_2O_3$ catalysts, in the preparation of which NaOH is used to precipitate the hydroxides, can be accounted for by the strong interaction of the metal with the carrier and the formation of Ni–Al compounds on the surface. However, similar catalysts formed under mild conditions, which rule out the formation of small nickel crystallites, have the same enantioselectivity as $Ni-SiO_2$.[116]

A series of studies by Izumi and coworkers[3,46,92] were devoted to the development of methods for increasing the enantioselectivity of the RNi–TA catalysts in the MAA hydrogenation reaction. With increase in the temperature of the leaching of the Ni–Al alloy, the optical activity of the product increases as a result of the decrease in the residual amount of aluminium present in the catalyst as aluminium hydroxide. The OH groups present in TA and $Al(OH)_3$ compete with one another for the formation of hydrogen bonds with MAA, reducing thereby *OY*. The elimination or blocking of the aluminium-enriched nickel centres increases the fraction of dissymmetric centres and increases *OY*. This view is confirmed by the fact that the nickel catalyst, obtained by the reduction of NiO in a stream of hydrogen at 523 K and modified with a 1% solution of TA at 358 K and pH 4.1, exhibits a higher enantioselectivity than the RNi–TA Raney catalyst. The hydrogenation of MAA in solution in EtCOOMe at a pressure of 1 MPa and a temperature of 393 K leads to the formation of (*R*)-(−)-MHB with *OY* = 81.7%, whereas the optical yield on RNi–TA under the same conditions is only 44%.[46]

The fraction of nonselective centres on the nickel surface may be diminished by the ultrasonic treatment of the catalyst, which induces the selective disruption of the more active centres not protected by the modifying agent, tartaric acid.[130] Such treatment makes it possible to increase not only *OY* but also the overall activity of the catalyst, i.e. to eliminate the disadvantage characteristic of RNi catalyst modified by TA in the presence of NaBr (as already stated, the adsorption of this salt increases *OY*, but decreases significantly the overall catalytic activity).

Table 9. Hydrogenation of the methyl esters of ketoacids on the RNi–TA–NaBr catalyst treated with ultrasound and the untreated catalyst (according to the data of Tai et al.[130]).

Compound hydrogenated	Treatment of a catalyst[a]	*w* /mmol min^{-1} (g catalyst)$^{-1}$	*OY*(%)
$MeCOCH_2COOMe$	+	18.0	86
	−	9.0	80
$n\text{-}C_7H_{15}COCH_2COOMe$	+	1.3	89
	−	0.3	83
$n\text{-}C_9H_{19}COCH_2COOMe$	+	0.9	91
	−	0.2	86
$n\text{-}C_{11}H_{23}COCH_2COOMe$	+	0.9	94
	−	0.2	86

Note. Reaction conditions: solvent — EtCOOMe, pressure 1 MPa, temperature 373 K.
[a] '+' — with treatment by ultrasound, '−' — without treatment by ultrasound.

The overall rate of hydrogenation after the ultrasonic treatment of the catalyst increases by a factor of 2–4, while *OY* increases to 86%–94% (Table 9). This is the maximum optical yield attained hitherto on modified RNi–TA–NaBr catalysts. After such treatment, the catalyst becomes stable and can be used to obtain the optically active (*R*)-(−)-MHB on a large scale. Thus it has been possible to hydrogenate 10 kg of MAA, dissolved in 100 dm^3 of EtCOOMe, on 190 g of the ultrasonically treated RN–TA–NaBr catalyst after 18 h. The optical yield of (−)-MHB in this reaction, carried out at a pressure of 10 MPa and a temperature of 373 K, was 81%.

Optically pure 100% MHB can be obtained by crystallising a MHB derivative — the dibenzylammonium salt of HBA.[130] For this purpose, (−)-MHB with an excess of the enantiomer (*OY* = 83%) is hydrolysed in a 1 : 1 $MeOH-H_2O$ mixture. The sodium salt is passed through a column with Amberlite IR-120 and the resulting acid (−)-HBA is converted into the dicyclohexylammonium[131] or dibenzylammonium salt,[130] which is then crystallised. This leads to the formation of the optically pure (*OY* = 98%–100%) acid (*R*)-(−)-HBA in a high yield (Table 10).

Table 10. Preparation of optically pure carboxylic β-hydroxyacids by the hydrogenation of the methyl esters of the β-ketoacids $Me(CH_2)_n$-$COCH_2COOMe$ on the RNi–TA–NaBr catalyst after three crystallisations of the dicyclohexylammonium salts of the acids from acetonitrile (according to the data of Tai and coworkers[131,135,136]).

n	*OY* for hydroxyester (%)[a]	Consumption of acetonitrile /ml (gram salt)$^{-1}$	β-Hydroxyacid	
			yield (%)	*OY*(%)[b]
0	86	7.0	52	98
6	87	11.5	50.5	98
8	88	18.0	73.5	100
10	85	19.0	72.1	100
12	87	24.5	75.1	98

[a] Before crystallisation. [b] After crystallisation.

An important practical problem concerns the possibility of the repeated use of the RNi–TA–NaBr catalysts. It has been shown that RNi–TA–NaBr introduced into a solid matrix of vulcanised silicone rubber containing oxime groups (KE-441 produced by the Shin Etsu Chemical Company) can be used repeatedly, up to 30 times, in the hydrogenation of MAA to (−)-MHB.[132,133] The optical yield on a single catalyst specimen (9 MPa, 373 K) is maintained at the level of 58%–62% and there is no significant decrease in enantioselectivity.[134] The usual catalyst without a matrix is somewhat more enantioselective but is less stable and *OY* has already decreased from 76% to 28% by the third experiment. The stability of the catalyst inserted into a silicone matrix is ensured by the binding of the nickel to the oxime groups of the polymer, which are converted into amino-groups during the reaction.[134] Treatment with a solution of pyridine or MePrNH[100,104] therefore also makes it possible to obtain a stable catalyst on one portion of which up to 10 consecutive hydrogenations can be performed with only a slight decrease in *OY* (from 80% to 73%).[134]

Processes in which the optical yield is not less than 80% while the preparation of the catalyst and the process technology are fairly simple are of practical interest. These requirements are satisfied by modified metallic catalysts. The industrial production of chiral hydroxyesters and glycols with *OY* up to 90% can be achieved on modified nickel catalysts.

The high effectiveness of the RNi–TA–NaBr catalysts has been used to synthesise practically important optically active β-hydroxyacids, which are common in biological systems. (*R*)-(−)-3-Hydroxydecanoic acid forms part of the composition

of growth factors, 3-hydroxytetradecanoic acid is the principal aliphatic acid in 'lipid A' in endotoxin,[135] the choline ester of 3-acetoxyhexadecanoic acid, known as pahutoxin, is one of the components of fish poison,[131,136] while 3-hydroxyoctadecanoic acid is a component of the antitumour preparation emposatilin. All these compounds have been obtained in high optical yields by the hydrogenation of the corresponding ketoacids on RNi–TA–NaBr at a pressure of 9.5 MPa and a temperature of 373 K in solution in EtCOOMe + AcOH. After 2–3 recrystallisations of the dicyclohexylammonium or dibenzylammonium salts, obtained from the esters of the corresponding hydroxyacids,[131,137] it is possible to obtain the optically pure acids in high yields. The nickel catalyst is also used in the synthesis of the hydroxyester which is an intermediate in the synthesis of tetrahydrolipostatin produced by the Hoffmann-LaRoche Company:[138]

$$Me(CH_2)_{10}COCH_2COOEt \longrightarrow Me(CH_2)_{10}CH(OH)CH_2COOEt \quad OY = 90\%-92\%$$

β-Hydroxyesters and β-glycols, for example ethyl β-hydroxybutyrate and pentane-(2*R*,4*R*)- and -(2*S*,4*S*)-diols, are produced industrially on the RNi–Ta–NaBr catalysts. The optical yield of the diol reaches 87%, while after the crystallisation of its derivative it becomes 100%.[139] This is used in the synthesis of the chiral diphosphine Skewphos [(*R*,*R*)-2,4-bis(diphenylphos-phino)pentane].[140]

Modified nickel catalysts for asymmetric hydrogenation are produced by the Wako Pure Chemistry,[141] Kawaken Pure Chemistry, and Degussa Companies (RNi–TA–NiBr)[138] and by the Heraeus Company (HNi–TA–NaBr).[138,142]

VI. Synthesis of optically active β-hydroxyesters by the hydrogenation of ketoesters on metal complex catalysts with chiral ligands

Chiral rhodium–diphosphine complexes are highly effective chiral catalysts on which it is possible to hydrogenate dehydroamino acids to optically active amino acids with *OY* close to 100%.[143] Under certain conditions, ketones can also be reduced on these catalysts.[143,144] The presence of the COOR group in the molecule facilitates reduction and hydroxyesters are formed from α- and β-ketoesters with high values of *OY*.[145] The ketoesters are particularly effectively reduced on chiral rhodium and ruthenium complexes.[146] The methyl acetoacetate is reduced to MHB with *OY* = 71% when acted upon by the complex [Rh–CAMP] [CAMP = (*R*)-cyclohexyl-*o*-methoxyphenylmethylphosphine].[147] The rhodium complex with the chiral diphosphine BINAP,[47,148] produced by the method of Takaya et al.,[149] exhibits a very high enantioselectivity. MAA is hydrogenated at pressures of 1.0 or 1.12 MPa and a temperature of 298 K for 48 h.[150,151] The (*R*)-(−)-β-hydroxyester with *OY* = 99% is formed from methyl β-ketovalerate in solution in 1:1 MeOH–CH_2Cl_2 in the presence of the complex [Rh–BINAP], and the optically pure (*R*)-(−)-hydroxyvaleric acid can be obtained by its hydrolysis.

The use of phospholanes as chiral ligands in rhodium complexes proved to be relatively ineffective: the optical yield did not exceed 27% in the reduction of MAA at a pressure of 2 MPa and a temperature of 298 K.[151]

VII. Conclusion

In conclusion, the three methods of synthesis of β-hydroxyesters examined above should be compared from the standpoint of their practical applicability. Table 11 presents the main characteristics of the processes involving the reduction of β-ketobutyrates, acted upon by baker's yeast, on a Raney nickel catalyst modified by (*R*,*R*)-tartaric acid with added NaBr, and in the presence of a chiral ruthenium complex containing a chiral ligand, the diphosphine BINAP.[32] As can be seen, all three methods ensure a high effectiveness of the process. The optical yield is 85%–99%. We shall now consider their disadvantages.

Despite the high enantioselectivity (in the best instances), the possibilities for wide scale application of the enzymic reduction of ketoesters are limited by the low productivity of the process, by the need to employ large volumes of solutions, by the low concentration of the product in solution, by the need for additional purification (filtration, extraction), by the long duration of the process, and by the instability of the enzyme. This is a single-use process which cannot be carried out under flow or cyclic conditions and the reducing agents are not regenerated.

The employment of a metal complex catalyst ensures an extremely high effectiveness and productivity, the turnover number for the reaction on such a catalyst being very high. The process can be performed at room temperature. However, the cost of the catalyst and of the chiral ligand is high and they cannot be regenerated.

Table 11. Comparative characteristics of various methods for the synthesis of β-hydroxybutyrates by the reduction of β-ketoesters.

Characteristic	Enzymic reduction [a]	Heterogeneous-catalytic process RNi–TA–NaBr	Metal complex catalysis Ru–BINAP
Substrate and its sample/g	EAA, 40	MAA, 40	MAA, 40
Solvent and its volume/ml	water, 2600	none	methanol, 40
Catalyst and its sample/g	baker's yeast, 200	Ni–TA–NaBr, 2	Ru–BINAP, 0.14
Reductant	sucrose (600 g)	hydrogen (75 atm)	hydrogen (20–100 atm)
Process temperature/K	293	373	293
Reaction time/h	134	20	40
Method for isolation of product	filtration, extraction, distillation	filtration, distillation	distillation
Chemical yield (%)	59–76	94	99
Chemical yield/g	24–30	38	39
Optical yield (%)	85	90	99
Configuration of molecule	*S* only	*S* or *R*	*S* or *R*
Productivity/g (litre solution)$^{-1}$ h^{-1}	0.07	40	12
Possibility of repeated use of catalyst	none	5–30 times	none

[a] Standard method.[45]

The somewhat reduced enantioselectivity of the heterogeneous catalyst modified by tartaric acid (the maximum optical yield attained so far is 94%) is compensated by the high productivity of the process, the possibility of the repeated employment of the catalyst (up to 30 times in certain cases), the ease of its separation from the product, and the low cost and ease of preparation of the catalyst. The heterogeneous catalyst can be readily prepared in large amounts and it can be usefully employed in the large-scale production of the chiral β-hydroxybutyrate with an optical yield of about 90%, particularly if it is proposed to carry out further purification of the product by the crystallisation of its derivatives.

Overall, chemical methods have clear advantages over enzymic procedures, which constitutes an important stimulus for the improvement of the latter. There is no doubt that further search for effective catalytic systems, both heterogeneous and metal complex, is needed.

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