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Advances in Asymmetric Hydrogenation. Catalytic Synthesis of Optically Active Hydroxy- and Amino-acids

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In the present review an attempt is made to follow the general relations in the formation of optical isomers and to elucidate the optimum conditions for the reactions on the basis of an analysis of the available literature data on the catalytic synthesis of aminoacids with reference to data on the hydrogenation of C=C and C=O bonds in optically active compounds. The extremely interesting and promising field of asymmetric hydrogenation using dissymmetrical heterogeneous catalysts, which requires special treatment, has been dealt with in the review only in connection with the synthesis of aminoacids. The bibliography includes 87 references.

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I. INTRODUCTION

Asymmetric hydrogenation has always attracted the attention of investigators as one of the methods for the preparation of optically active compounds by the addition of hydrogen to the multiple bonds C=C, C=O, and C=N, in the presence of an asymmetrising agent (an optically active group in the molecule, a dissymmetric catalyst). Recently there has been a particular growth of interest in asymmetric hydrogenation in connection with the application of new methods for the synthesis of optically active α-aminoacids.

The advances in asymmetric hydrogenation have not yet been reflected in an adequate compilation of the relevant studies. There are only a few obsolete reviews [1,2] in Japanese.

Asymmetric catalysis is based on the concept of the *cis*-addition of hydrogen from the catalyst surface, which has been expressed quantitatively in Balandin's multiplet theory of catalysis and theory of hydrogenation. According to the multiplet theory, the addition of hydrogen to the molecule of an unsaturated compound takes place in a reaction sphere of minimum volume without the desorption of the intermediate semihydrogenated species from the catalyst surface. The presence of the heterogeneous catalyst surface gives rise to additional steric hindrance in this process and promotes its stereospecificity.

The formation of optically active compounds in asymmetric heterogeneous catalytic hydrogenation confirms the mechanism of *cis*-addition, since otherwise, in *trans*-addition or for desorption of the semihydrogenated species, the racemate would be formed in the bulk phase. At the same time these data show that, under the conditions investigated, the impact hydrogenation mechanism is unlikely and it must be assumed, in accordance with the multiplet theory, that the reaction takes place in direct contact with the catalyst. According to Balandin's hydrogenation theory [3], the activation of the compound hydrogenated B and hydrogen H takes place at different centres K' and K respectively, and the centre K may be subdivided further into centres A which are responsible for the separate adsorption of hydrogen atoms. Then the stages in the attainment of adsorption equilibrium at the two types of centre are represented by mechanisms (1) and (2) and the rate-limiting stage of the process is represented by mechanism (3):

$$B + K' \rightarrow BK';\ H_2 + K' \rightarrow H_2K';\ C + K' \rightarrow CK', \quad (1)$$

$$B + K \rightarrow BK;\ H_2 + K \rightarrow H_2K \rightarrow 2(H \cdot A);\ C + K \rightarrow CK, \quad (2)$$

$$BK' + HA \rightarrow XK'A;\ XK'A + HA \rightarrow CK' + K, \quad (3)$$

where C is the reaction product and X the semihydrogenated species, which is not released into the bulk phase from the catalyst surface and which undergoes all transformations on the surface. The adsorption of compound B (to be hydrogenated) at centres K' [mechanism (1)] and the rate-limiting stage [mechanism (3)] must take place on the sterically least hindered side of the molecule, which determines the stereochemistry of the product.

The occurrence of asymmetric synthesis is due to the difference between the rates of formation of the optical isomers of the product C from the initial compound B:

$$B \begin{cases} \xrightarrow{k_d} (+)\,C \\ \xrightarrow{k_l} (-)\,C \end{cases},$$

which is determined by the difference between the free energies of activation $\Delta F^{\neq}$ for the diastereoisomeric transition states. According to the transition state theory, the specific rate of formation of one of the optical isomers, for example, the (+)-isomer, is defined as follows:

$$k_d = \frac{kT}{h} e^{-\frac{\Delta F_d^{\neq}}{RT}}.$$

For two competing reactions involving the formation of the (+)- or (−)-isomers, we have, $k_d/k_l = C_d/C_l$ and for a transmission coefficient close to unity the ratio of the rate constants for the formation of the (+)- and (−)-isomers is

$$\ln \frac{k_d}{k_l} = \ln \frac{C_d}{C_l} = \left(\frac{\Delta S_d^{\neq}}{R} - \frac{\Delta H_d^{\neq}}{RT}\right) - \left(\frac{\Delta S_l^{\neq}}{R} - \frac{\Delta H_l^{\neq}}{RT}\right) =$$

$$= \left(\frac{\Delta S_d^{\neq}}{R} - \frac{\Delta S_l^{\neq}}{R}\right) - \left(\frac{\Delta H_d^{\neq}}{RT} - \frac{\Delta H_l^{\neq}}{RT}\right) = \frac{\Delta\Delta S_{d-l}^{\neq}}{R} - \frac{\Delta\Delta H_{d-l}^{\neq}}{RT},$$

where the enthalpy of activation $\Delta H^{\neq}$ is related to the experimentally determined activation energy E by the equation

$$\Delta H^{\neq} = E - RT.$$

Low values of $\Delta\Delta S^{\neq}$ indicate a similarity of the structures of the diastereoisomeric transition states.

The specific rotation of the product is determined from the expression

$$\alpha_D^t = \alpha_{obs} \times 100/lC,$$

where α_{obs} is the observed optical rotation in a layer of length l (in decimeters) at a concentration C (1 g per 100 ml solution). The molecular rotation $[M]_\lambda^t$ is defined thus:

$$[M]_\lambda^t = [\alpha]_\lambda^t \frac{M}{100}.$$

The optical purity (P, %), also called the optical yield or the asymmetric yield, is defined by the ratio of $[\alpha]_D$ found for the product to the maximum specific rotation quoted in the literature $[\alpha]_{D(lit.)}$ for the optically pure compound:

$$p = \frac{[\alpha]_{D(found)}}{[\alpha]_{D(lit)}} \cdot 100 = \frac{[M]_{D(found)}}{[M]_{D(lit)}} \cdot 100.$$

The specificity Sp_+, or the ratio of the fraction of one optical isomer to the other in a given compound, determined from the expression

$$Sp_+ = \frac{[(+)\text{-isomer}]}{[(-)\text{-isomer}]} = \frac{100+p}{100-p},$$

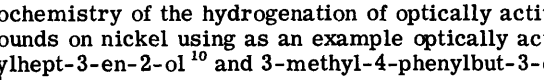
varies in the range $\infty \geq Sp \geq 1$.

Two methods are employed at present for the determination of the optical purity of the compound. The first requires the separation of the optical isomers in a pure form or in the form of their diastereoisomers. This procedure includes, apart from the classical method of the isolation of usually one optical isomer by the recrystallisation of the diastereoisomers, the method of isotope dilution [4], a kinetic method [5], and an enzymatic method. In the second procedure it is sufficient to determine analytically the ratio of the diastereoisomers, for example by gas–liquid chromatography (Weygand [6], Belikov and coworkers [7]) or by NMR (Raban and Mislow [8,9]).

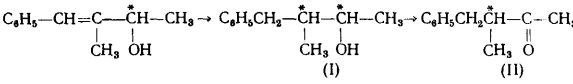
The stereochemistry of the asymmetric hydrogenation of C=C and C=O bonds, on which extensive data have accumulated recently, provides valuable information for the understanding of the catalytic synthesis of optically active aminoacids.

II. HYDROGENATION OF OPTICALLY ACTIVE UNSATURATED AND CARBONYL COMPOUNDS

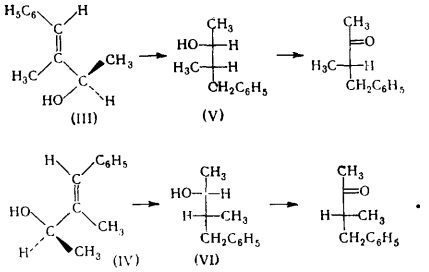
Arcus and coworkers [10–12] made a detailed study of the stereochemistry of the hydrogenation of optically active compounds on nickel using as an example optically active 3-ethylhept-3-en-2-ol [10] and 3-methyl-4-phenylbut-3-en-2-ol [11]. The initial asymmetric centre in the molecules is destroyed by oxidising the hydrogenation product to the corresponding ketone by the mechanism



The experimental results showed that in the hydrogenation of (−)- and (+)-3-ethylhept-3-en-2-ol there is partial asymmetric synthesis with an optical yield of 76 and 36% of the (+)- and (−)-ketones respectively. The authors explained this finding by postulating that the substrate molecule is oriented with respect to the catalyst surface predominantly in the sterically least hindered conformation. The stereochemistry of the transition state has been examined in the hydrogenation of (−)-3-methyl-4-phenylbut-3-en-2-ol [11]. In this case the product is (+)-3-methyl-4-phenylbutan-2-ol and, after oxidation of the alcoholic group with chromium trioxide, (−)-3-methyl-4-phenylbutan-2-one:



We shall consider the structure of the transition state on the surface of the catalyst. The molecule of *trans*-3-methyl-4-phenylbut-3-en-2-ol can be adsorbed in conformations (III) or (IV) (the plane of the figure corresponds to the catalyst surface):

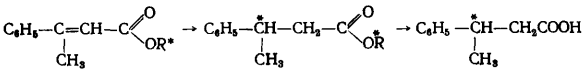


In the hydrogenation of (III) and (IV) hydrogen approaches from behind the plane of the figure with formation of the diastereoisomers (V) and (VI). It is postulated that the adsorption of the molecule in conformation (III) is the most probable, since in conformation (IV) the two bulky methyl groups are located too close to one another. Since the specific rotation of the pure diastereoisomers (I) and the ketones (II) was unknown, the degree of asymmetric synthesis (more precisely "dissymmetric synthesis") was estimated by quantitative gas-chromatographic analysis of the diastereoisomeric alcohols and, in two experiments, from the hydrogenation of (−)-3-methyl-4-phenylbut-3-en-2-ol and was found to be 22 and 17%.

The hydrogenation of racemic *trans*-4-phenylpent-3-en-2-ol [12] in conformations corresponding to (III) and (IV) gives a mixture of the four possible diastereoisomers, which consist of two pairs of optical isomers. The degree of dissymmetric synthesis in the two experiments proved to be 50 and 57% respectively. The proposed method, based on the chromatography of diastereoisomers, is extremely promising in the study of the stereochemistry of the reactions of various compounds, since there is no need to determine the optical activity of the product and it is possible to employ racemic compounds.

It was noted long ago that the stereochemistry of the activating optically active group determines to a considerable degree the effectiveness of asymmetric catalysis.

In the hydrogenation of optically active esters of β-methylcinnamic acid on platinum black, Vavon and Yakubovicz [13] obtained, after hydrolysing the hydrogenation products, optically active β-phenylbutyric acid with different degrees of optical purity:

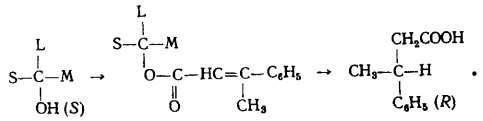


Menthol, neomenthol, *cis*- and *trans*-carvomenthols, and 3α- and 3β-cholestanols were employed as the optically active alcohols. The highest optical yield (20%) of β-phenylbutyric acid was obtained when menthol was employed.

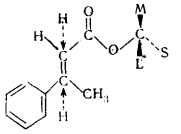
Hydrogenation of hydrocinchoninium salts of β-methyl and β-(α′-naphthyl)cinnamic acids on platinum oxide gave

β-phenylbutyric acid with $[\alpha]_{546} = +4.5°$ and an optical yield of 9% and β-(α'-naphthyl)-β-phenylpropionic acid with $[\alpha]_{546} = -0.5°$. The stereochemistry of the catalytic hydrogenation of β-methylcinnamic acids was examined in detailed by Prelog [14,15].

The stereochemistry of asymmetric hydrogenation is determined by the difference between the sizes of the substituents at the asymmetric carbon atom in the activating alcohol. An increase of the difference between these sizes leads to an increase of the optical yield of the reaction. If L, M, and S are respectively large, medium, and small substituents at the asymmetric carbon atom, then the configurations of the optically active alcohol and the optical isomer of β-phenylbutyric acid obtained in excess are related as shown in the scheme below [i.e. under the conditions investigated, the (*S*)-configuration of the alcohol promotes the formation of the (*R*)-configuration of the acid]:



Examination of the conformation of the molecule of β-methylcinnamic acid shows that all the atoms, except the substituents L, M, and S, lie in the same plane. Hydrogen attacks the double bond from the sterically least hindered side, i.e. from the side of the small substituent S:



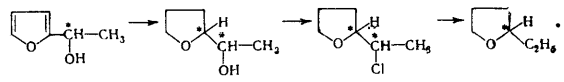
This should result in the formation of (−)-(*R*)-β-phenylbutyric acid. Table 1 shows that this mechanism, based on Prelog's rule, does indeed hold in the hydrogenation of the menthyl and bornyl esters of β-methylcinnamic acid. However, in the hydrogenation of neocarvomenthyl and 3α-cholestanyl esters Prelog's rule does not hold. It may be supposed that the rigid configuration of the molecule, which hinders the catalytic process, has an effect in this case. This is clearly shown, for example, in the hydrogenation of bicyclic compounds with bridged systems. Thus the hydrogenation of (+)-α-pinene on Raney nickel (*W*-3) in ether at 107°C and 100 atm results in the formation of almost exclusively *cis*-pinane, because α-pinene is adsorbed on the catalyst in such a way that the isopropylidene bridge is directed away from the catalyst [12]:



Prelog and coworkers [15] showed that the asymmetric yield of β-phenylbutyric acid depends also on the experimental conditions. Thus, in the hydrogenation of the ester of β-methylcinnamic acid and t-butylmethylmethanol on Raney nickel, Pd/C, and PtO_2 in acetic acid, the optical yield was greatest in the last case.

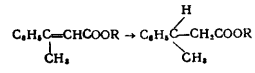
The degree of asymmetric synthesis is also influenced by the location of the dissymmetric centre in the molecule. The greatest asymmetrising effect of this centre may be expected when it is adjacent to the reacting group. Vavon [13] explained the low degree of asymmetric synthesis in the hydrogenation of optically active β-methylcinnamic esters by the remoteness of the optically active group from the group of reacting atoms.

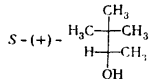
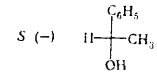
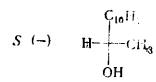
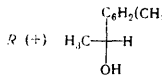
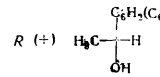
The remoteness of the asymmetric centre in the ester precludes racemisation, whereas the racemisation at the α-asymmetric carbon atom proceeds extremely readily. This can account for the failure of the attempt at asymmetric synthesis in the preparation of a furan derivative by the hydrogenation on nickel of optically active furylmethylmethanol, which was undertaken by Duveen and Kenyon [16] on the basis of the mechanism



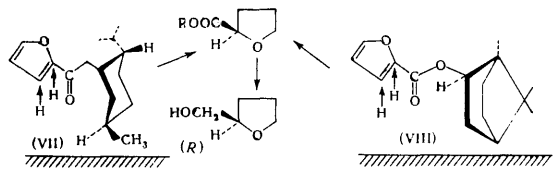
The product obtained after the removal of the initial asymmetric centre proved to be optically inactive. It is also possible that the choice of reaction conditions was inappropriate.

Table 1. Asymmetric hydrogenation of β-methylcinnamic acid esters.



R	Optical rotation of product: established in Ref.13, deg	Optical rotation of product: sign of rotation predicted by Prelog's rule	Optical yield of acid, %
S-(+)- 	− 4.7	(−)	8.5
S (−) 	− 2.5	(−)	4.5
S (−) 	− 4.2	(−)	7.5
R (+) 	+ 7.5	(+)	13
R (+) 	+15.5	(+)	27
(−)-(*R*)-mentol	+12	(+)	21
(+)-(*S*)-neomenthol	− 4.9	(−)	8.6
(+)-*trans*-carvomenthol	− 1.8		3.1
(−)-(*R*)-*cis*-carvomenthol	− 3.2	(+)	5.8
3-α-cholestanol	− 3	(+)	5.2
3-β-cholestanol	− 2.3		4.0

Asymmetric hydrogenation of the furan ring was achieved by Godunova, Klabunovskii et al. [17] by the mechanism



from (−)-menthyl (VII) and (−)-bornyl (VIII) esters of furancarboxylic acid. On the $Pd(OH)_2/C$ catalyst, the

hydrogenation (150 atm, 20°C) takes place stereospecifically with formation of about 20% of an excess of the (*R*)-isomer. The ester of tetrahydrofurancarboxylic acid is reduced by $LiAlH_4$ to an alcohol, which is characterised by a positive optical rotatory dispersion curve. Examination of the stereochemistry of the transition states (VII) and (VIII) in accordance with Prelog's rule shows that (−)-(*R*)-menthol and (−)-(*R*)-borneol lead to tetrahydrofuryl alcohol with the same (*R*)-configuration as the product.

The stereochemical concepts based on Prelog's rule have been increasingly adopted in catalysis in recent times but one must consider the following important factor, which makes it necessary to employ this rule with caution. As stated above, asymmetric catalysis is due to the differences between the free energies of activation for diastereoisomeric transition states. When the difference between these quantities for the (+)- and (−)-products is large, a sharp difference may be expected between the curves relating the optical yields of the two optical isomers to reaction temperature.

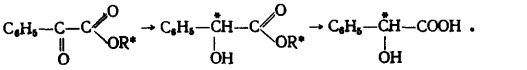
Pracejus [18] showed experimentally that the asymmetric yield of methyl β-phenylpropionate in the reaction of methylphenylketen with methanol promoted by acetylquinine as a dissymmetric catalyst increases sharply when the reaction temperature is reduced and that at −111° it reaches 74%, which corresponds to $Sp = 6.6$. The (−)-(*R*)-ester is formed almost 7 times faster than the (+)-(*S*)-isomer with $\Delta\Delta H^{\neq}_{R\text{-}S} \simeq -2.8$ kcal mole^{-1} and $\Delta\Delta S^{\neq}_{R\text{-}S} = -13$ cal mole^{-1} deg^{-1}. Hence it follows that $\Delta H^{\neq}_{S}$ of the sterically more hindered reaction leading to the formation of the (+)-(*S*)-isomer is higher by about 2.8 kcal mole^{-1} than for the reaction with formation of the (−)-(*R*)-isomer and the entropy of activation $\Delta S^{\neq}_{S}$ for the (+)-(*S*)-isomer exceeds by 13 e.u. $\Delta S^{\neq}_{R}$ for the (−)-(*R*)-isomer.

These data confirm the theoretical postulates and show that stereospecific catalysis, in which the entropy factor plays an important role, takes place above the isokinetic temperature [19] where a compensation effect [simultaneous increase (or decrease) of $\Delta H^{\neq}$ and $\Delta S^{\neq}$] is observed.

The above data show at the same time the importance of studying the temperature variation of the asymmetric reaction, since the change in the sign of the optical rotation and of the optical yield of the product at an arbitrary temperature (such as, for example, the temperature at which the Grignard reaction was carried out in Prelog's experiments) may lead to incorrect conclusions concerning the configurational relations. Therefore Prelog's method for the determination of such relations is applicable only for high differences between the free energies of activation for the diastereoisomers investigated and for fairly high optical yields. These limiting conditions still await experimental confirmation.

In the catalytic synthesis of optically active compounds and in the determination of the configuration, the stereochemical relations are complicated still more by the effect of the nature of the catalyst and of adsorption on its surface. This is seen from the hydrogenation of keto-compounds as an example.

The catalytic hydrogenation of α-ketoacids esterified by certain optically active alcohols was investigated by Mitsui and coworkers [20–25]. They chose for investigation benzoylformic acid, the asymmetric reduction of which by aluminium amalgam and other agents had been studied previously. The heterogeneous catalytic hydrogenation of optically active esters of benzoylformic acid was carried out on metallic catalysts (Raney nickel, PtO_2, Pd/C, $Pd/CaCO_3$, and $Pd/BaSO_4$). The experimental results showed (Table 2) that the hydrogenation of (−)-menthyl [20] and (+)-bornyl [21] esters with subsequent hydrolysis yield optically active mandelic acid:



However, it was found that the sign of the rotation of the product is almost independent of the nature of the catalyst employed and is wholly determined by the presence on the catalyst surface of traces of acid or alkali, which may be inferred from the procedure employed in the preparation of the catalyst.

When catalysts containing traces of a base (B), such as PtO_2, Raney nickel, and Pd/C–B were used, (−)-menthyl (−)-mandelate and (+)-bornyl (+)-mandelate were obtained respectively; after hydrolysis they yielded (−)- and (+)-mandelic acids. On the other hand, the hydrogenation of the above esters under the same conditions on "acidic" catalysts (A) gave (+)- and (−)-mandelic acids. The reduction of cholesteryl esters of benzoyl formic acids on "acidic" and "alkaline" catalysts leads to racemic mandelic acid [21]. In the hydrogenation of (−)-α-phenylethyl ester of benzoylformic acid [22] the sign of the rotation of mandelic acid depends on the nature of the surface of the catalyst employed [22]; namely on "alkaline" and "acidic" catalysts the (+)- and (−)-mandelic acids were obtained (Table 2). However, the reduction of the (−)-α-phenylethylamide of benzoylformic acid was unaffected by the nature of the catalyst surface; the laevorotatory hydroxyacid was obtained in both cases [22].

To elucidate the influence of substituents in the ester molecule on the mechanism of the asymmetric reduction of α-ketoacids under the conditions of heterogeneous catalysis, a study was made of the hydrogenation of (−)-menthyl esters of certain other α-ketoacids: pyruvic, t-butylglyoxylic [23], and α-naphthylglyoxylic [24,25]. It was found that the ester of α-naphthylglyoxylic acid behaves in this reaction like the ester of benzoylformic acid, i.e. on "acidic" (platinum with added hydrochloric acid etc.) and "alkaline" catalysts, the (+)- and (−)-α-naphthylglyoxylic acids were obtained [24]. On the other hand, the sign of the rotation of the lactic and t-butylglyoxylic acids was independent of the nature of the catalyst surface [23]. In the reduction of (−)-menthyl esters of the corresponding α-ketoacids, the (+)-hydroxyacids were always obtained (Table 2).

The interpretation of the results from the standpoint of Prelog's rule showed that the hydrogenation of (−)-menthyl benzoylformate on "alkaline" catalysts presupposes the *trans*-conformation (IXa) of the group $-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}$, while on "acidic" catalysts it is necessary to postulate the *cis*-conformation (IXb):

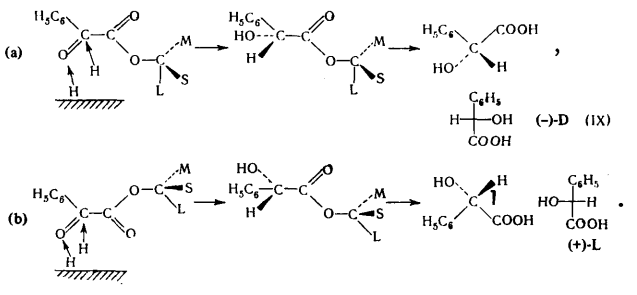
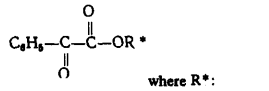
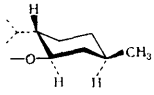
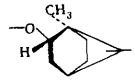
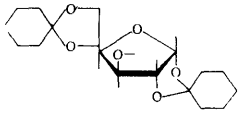
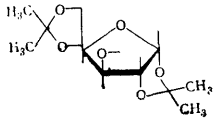
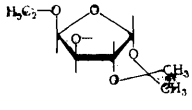
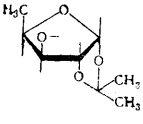
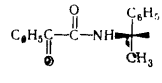
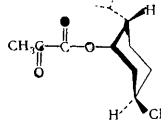
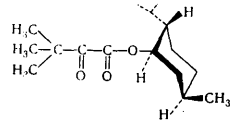
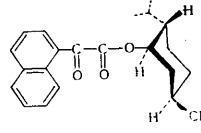
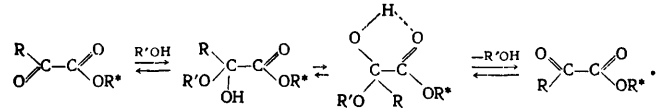


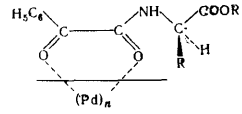
Table 2. Dependence of the configuration of the hydrogenation product on the nature of the catalyst[20–25,27].

Substrate	Reaction product: hydroxyacid formed	configuration, sign of rotation, optical yield (%), and most effective catalyst: "acidic"	"alkaline"
 where R*:	mandelic acid		
(a) (–)-(*R*)-menthyl 	ditto	(+)-L; 16.8% 5% Pd/C—B+ +HCl	(–)-D; 21.7% PtO_2
(b) (+)-(*S*)-bornyl 	»	(–)-D; 7.2% 5 %Pd/C+ +HCl	(+)-L; 22.9% PtO_2
(c) cholesteryl	»	0 %	0 %
(d) (–)-D-α-phenylethyl 	»	(–)-D; 2.4% Pd/C—A	(+)-L; 3.6%, Ni
(e) sugar derivatives 	»	(+)-L; 24.1 5% Pd/C—A	(–)-D; 44.6% Raney Ni
	»	(+)-L; 20.3% 5% Pd/C—A	(–)-D; 36.7% Raney Ni
	»	(+)-L; 9.4% 5% Pd/C—A	(–)-D; 19.9% Raney Ni
	»	(+)-L; 12.8% 5% Pd/C—A	(–)-D; 14.0 Raney Ni
	mandelic acid	(–)-D; 10.8% Pd black	(–)-D; 25.0 Ni
	(+)-L-lactic acid	(+)-L; 22% Pd/C—A	(–)-L; 33% PtO_2
	(+)-t-butyl glycolic acid	(+); 17% Pd/C—A	(+); 41% PtO_2
	naphthyl-glycolic acid	(+)-D; 16.5% Pd, $Pd(OH)_2/C$	(–)-L; 54.6% PtO_2

The formation of this energetically less favourable *cis*-conformation can be accounted for by the presence of a hydrogen bond between the carbonyl groups:



In the reduction of the (–)-α-phenylethylamide of benzoylformic acid the configuration of the reaction product is independent of the nature of the catalyst; the laevorotatory mandelic acid was always obtained. Consequently the optically active acid amide reacts preferentially in the *cis*-conformation (IXb) in the presence of both "acidic" and "alkaline" catalysts. Harada and Matsumoto[26], who investigated the hydrogenation on Pd/C of the amide derivatives of benzoylformic acid with the general formula $C_6H_5-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}NH-\underset{\underset{COOR}{\diagdown}}{\overset{\overset{R}{\diagup}}{CH}}$, confirmed the hypotheses of Mitsui and coworkers[22]. According to the authors' postulate, the *cis*-conformation of the molecule is stabilised by the formation of a five-membered cyclic complex with the catalyst:



On the other hand, the (–)-menthyl esters of pyruvic and t-butylglyoxylic acids probably react predominantly in the transoid conformation (IXa)

Kawana and Emoto[27] used certain monosaccharide derivatives as asymmetrising agents. The hydrogenation of the corresponding esters of benzoylformic acid on Pd/C–A, Pd/C–B and Raney nickel gave the optically active hydroxyacids after hydrolysis. Under the conditions of "alkaline" catalysts (Pd/C–B, Raney nickel), (–)-D-mandelic acid is the product, while the use of an "acidic" catalyst Pd/C–A gives (+)-L-mandelic acid. These and other results discussed above are compiled in Table 2, which shows that the configuration of the hydroxyacid formed depends on the nature of the surface of the catalyst employed and on the conformation in which the substrate is preferentially adsorbed on the catalyst surface.

The optical purity of the product is influenced by other factors, such as, for example, the chemical nature of the catalyst employed, the solvent, the duration of hydrogenation, and the time during which the solution is kept before hydrogenation. The use of a series of different catalysts showed that the most effective of the "acidic" catalysts is 5% Pd/C–A with added hydrochloric acid—the optical yield then reaches $p = 24\%$, while with "alkaline" catalysts the maximum asymmetric yield was obtained on the PtO_2 catalyst: $p = 54.6\%$, which exceeds by a factor of 8–10 the asymmetric yield found in the presence of homogeneous catalysts of this reaction. Since the addition of acid or alkali to the catalyst leads to a change of the optical purity of the isomer formed in excess, it would be extremely important to investigate the effect of the pH of the medium on the stereospecificity of the process.

An interesting variation of the asymmetric yield with the solvent employed has been noted (Table 3).

If the solution tested is kept for several hours before hydrogenation, the optically active acid obtained is more laevorotatory than the acid formed by the hydrogenation of the solution without preliminary standing. These results

can be accounted by the mutarotation of the benzoylformic acid esters. Indeed Glazer and Turner[28], who investigated the mutarotation of the above esters, showed that the equilibrium optical rotation of the esters decreases with decrease of the dielectric constant of the solvent empolyed (Table 4).

Table 3. Optical rotation of mandelic acid obtained in the hydrogenation of (−)-menthyl benzoylformate in various solvents.

Catalyst	Solvent					
	methanol	ethanol	1-propanol	2-propanol	ether	benzene
Alkaline PtO_2	−18.8	−4.3	−45.4	−42.5	−37.0	−47.2
Acidic 5% Pd/C-A	+ 8.3	+4.2	+17.0	+ 8.3	+ 5.6	+ 6.0

Evidently the observed sequence (with certain exceptions) is the reverse of that presented in Table 3. This indicates a possible relation between the effectiveness of the catalytic asymmetric synthesis of mandelic acid and the degree of mutarotation of menthyl phenylglyoxylate in the corresponding solvent; the greater the degree of mutarotation, the lower the purity of the product. Consequently, an increase of the polarity of the solvent lowers in this case the effectiveness of the asymmetric synthesis.

Table 4. Variation of the specific rotation of (−)-menthyl benzoylformate with the solvent[28].

$[\alpha]_{5461}^{25}$	Solvent			
	methanol	ethanol	1-propanol	2-propanol
Initial	−54	−54	−54	−52
Equilibrium	−75	−60	−61	−52
Δ	21	8	7	0

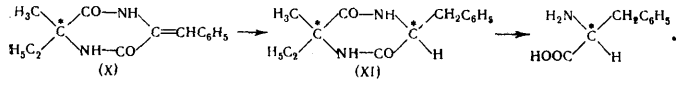
The same relation in the synthesis of aminoacids was observed by Harada and Matsumoto[29] (for a more detailed description, see p. 1044). So far the results presented in Table 2 do not allow definite conclusions concerning the correlation between the configurations of the asymmetric alcohol and the hydroxyacid formed. The results require further revision and in particular a study of the dependence of asymmetric yield on temperature, pH, and the solvent.

III. CATALYTIC ASYMMETRIC SYNTHESIS OF α-AMINOACIDS

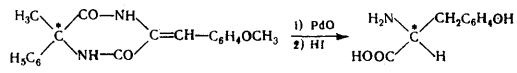
1. Hydrogenation of C=C Bonds in Optically Active Compounds

Optically active α-aminoacids may be obtained by the catalytic reduction of the C=C bond in dehydro-α-aminoacids in the presence of an asymmetrising agent. The number of examples of such asymmetric syntheses in the literature is fairly large[30-35].

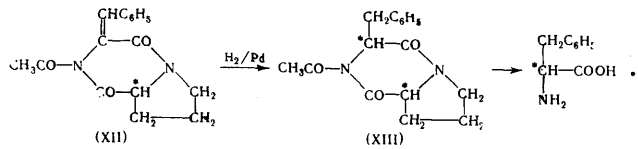
Akabori and coworkers[30,31] obtained L-phenylalanine with $[\alpha]_D^{21} = -34.0°$ by the hydrogenation over platinum oxide of the mixed anhydride of dehydrophenylalanine and L-isovaline (X). The asymmetrising agent (L-isovaline) was then eliminated in the hydrolysis of the diastereoisomer (XI) formed:



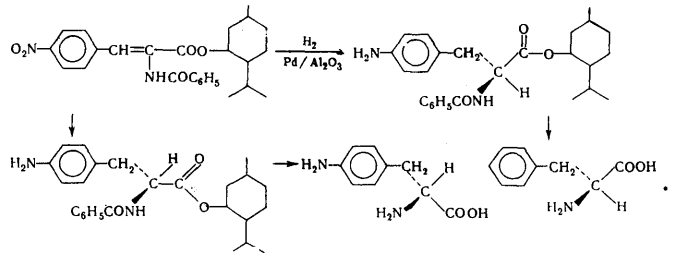
Maeda[32], who employed (+)-D-α-amino-α-phenylpropionic acid instead of isovaline, carried out a similar asymmetric synthesis and obtained L-tyrosine in 35% optical yield:



Bergman and Tietzmann[33] reduced the optically active dioxopiperazine formed by *N*-acetyldehydrophenylalanyl-L-proline (XII) over palladium black and obtained a 50% yield of the cyclic dimer of *N*-acetyl-L-phenylalanyl-L-proline (XIII) with $[\alpha]_D^{22} = \pm 202.6°$ and after its hydrolysis L-phenylalanine with $[\alpha]_D^{27} = -33.9°$:

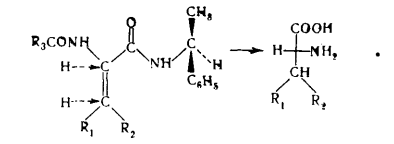


Pedrazzolli[34] achieved an asymmetric synthesis involving the catalytic dehydrogenation of the C=C bond over Pd/Al_2O_3 by reducing the (−)-menthyl ester of α-benzamido-*p*-nitrocinnamic acid and obtained a mixture of diastereoisomers. The separation of the latter showed that the (*SR*)-diastereoisomer is present in excess, with (*SR*) : (*RR*) = 68 : 32. After the hydrolysis of the hydrogenation products to *p*-aminophenylalanine, it was found that the degree of asymmetric synthesis is $p = 34\%$. When the bornyl ester was employed, the final product proved to be optically inactive:



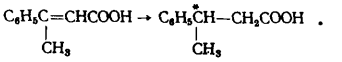
Sheehan and Chandler[35] carried out the asymmetric synthesis of valine and phenylalanine by the catalytic hydrogenation on Raney nickel of the optically active alkylamides of α-acetamido-β-methylcrotonic and α-benzamidocinnamic acids. Optically active α-phenylethylamine was employed as an asymmetrising agent. In accordance with Prelog's rule, when (−)-phenylethylamine is employed [provided one adopts for the (−)-amine the configuration indicated in the scheme], the products are

(−)-D-valine and (+)-D-phenylalanine, while the use of (+)-phenylethylamine leads to their optical isomers:



1) $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = C_6H_5$; (−)-D; $p = 18\%$
2) $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$; (−)-D; $p = 39\%$
3) $R_1 = C_6H_5$, $R_2 = H$, $R_3 = C_6H_5$; (+)-D; $p = 6\%$

The first data on the asymmetric reduction of β-methylcinnamic acid by hydrogen transfer were quoted by Lipkin and Stewart [36,37]; the use of Raney nickel in the presence of D-glucose led to β-phenylbutyric acid with $\alpha_D = 0.42°$ ($p = 5\%$):



By reducing acetamido- and benzamido-cinnamic acids on Raney nickel in the presence of glucose, Nakazaki [38] obtained phenylalanine in a very low optical yield (Table 5):

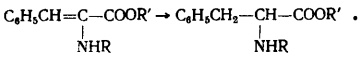


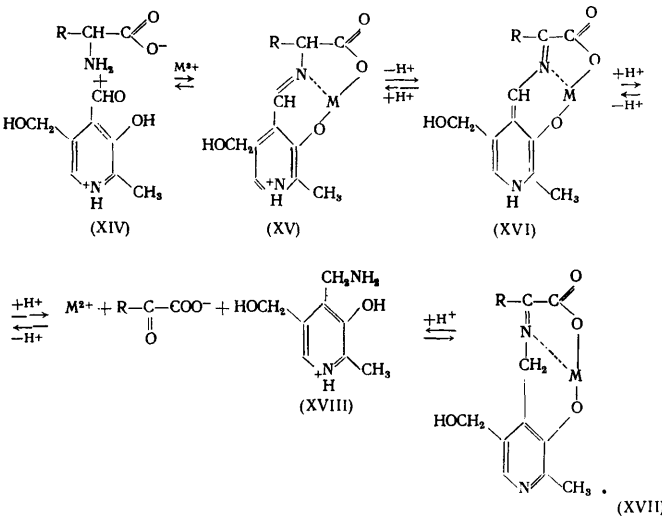
Table 5. Reduction of acylaminocinnamic acids on nickel in the presence of glucose.

R	Acid, g	Glucose, g	Ni, g	Reaction temp., °C	Phenylalanine	
					α_D, l2	$[\alpha]_D$
CH_3CO	4.1	7.9	0.8	30	−0.02	−2.22
CH_3CO	3.9	7.7	1.0	24	+0.03	+3.26
C_6H_5CO	4.0	5.9	1.0	28	+0.02	+1.96

The author interpreted the results as asymmetric reduction with hydrogen transfer, in which glucose is a hydrogen donor and the nickel catalyst an activator and hydrogen-transferring agent. However, the reliability of the data obtained is extremely doubtful, since the observed rotations are within the limits of the error of the measurement.

2. Preparation of Aminoacids by the Reduction of the C=N Bond

A large number of facts indicate a significant role of the C=N bond in biochemical processes. Although many details of enzymatic reactions are still not clear, certain simplest enzyme systems with a C=N group have been thoroughly investigated. Snell and coworkers [39] proposed a fairly simple mechanism for the transfer of the aminogroup from an aminoacid to a ketoacid catalysed by pyridoxal in the presence of certain complex-forming metals:

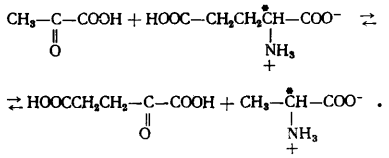


(XIV) (XV) (XVI) (XVIII) (XVII)

The reverse transfer by the reaction of pyridoxamine (XVIII) with the ketoacid is possible via the intermediate states (XVII) → (XVI) → (XV); as a result pyridoxal (XIV) is regenerated.

The catalytic methods for the synthesis of optically active aminoacids by the hydrogenation of compounds containing the azomethine group C=N can be divided into three types: (1) enzyme-catalysed transamination of optically inactive aminoacids and ketoacids; (2) transamination of ketoacids and optically active aminoacids; (3) reductive transamination of ketoacids in the presence of optically active amines.

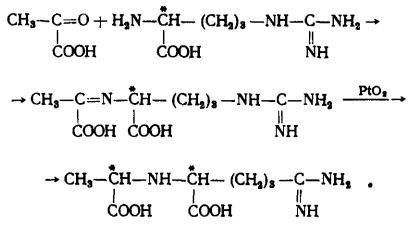
In reactions of the first type the enzyme plays the role of an asymmetrising agent, which probably forms intermediate complexes analogous to (XV) ⇌ (XVI) ⇌ (XVII). For example, L-alanine and α-oxoglutaric acid react in the presence of muscle tissue enzymes, forming pyruvic and L-glutamic acids [40,41]. The reaction between pyruvic and L-glutamic acid catalysed by pyridoxal phosphate and an enzyme leads to the formation of L-alanine [42]:



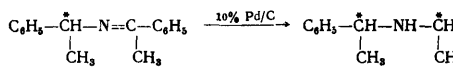
An aminoacid in an optically active form can have a similar asymmetrising effect in the reaction; however, the degree of asymmetric activation is usually low. Thus the reaction of L-alanine or L-phenylalanine with α-oxoglutaric acid catalysed by copper-pyridoxal phosphate gives rise to glutamic acid [43] in which the ratio of the L- and D-isomers is 55 : 45. In this case the asymmetric synthesis takes place as a result of the formation of dissymmetric intermediate chelates, which may be protonated stereospecifically.

The third type of asymmetric synthesis of aminoacids is achieved when an optically active aminoacid or amine is employed as the asymmetrising agent. Thus the hydrogenation on PtO_2 of a mixture of L-arginine and pyruvic acid in aqueous solution gives octopine $\{[\alpha]_D^{20} = +22.3°\}$. [44,45]

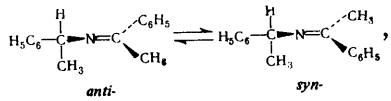
It is suggested that the mechanism of this reaction consists in the reduction of an intermediate Schiff base [46]:



The hydrogenation on Pd/C of the Schiff base obtained from acetophenone and α-phenylethylamine $\{[\alpha]_D^{25} = -40.5°\}$ results in the formation of an almost pure optically active product (p = 97.5%) and not a mixture of the optical isomer and the meso-form [47]:

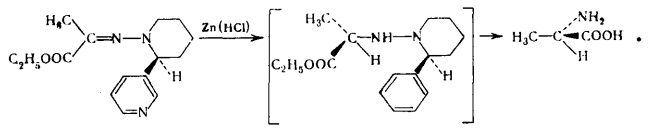


This result can be explained by the fact that in the initial compound, which is an equilibrium mixture of two *syn*- and *anti*-isomers,

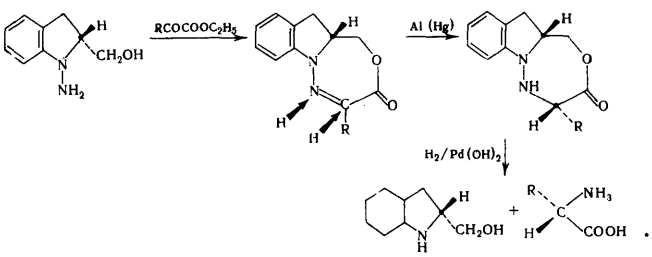


the less stable *syn*-isomer is hydrogenated at a higher rate, which leads to the optically active amine.

A method based on the reduction of the azomethine bond in the system C=N–N– with subsequent dissociation of the N–N bond was employed by Akabori [48,49] and Kost et al. [50] When α-ethoxycarbonylethylidene-*N*-aminoanabasine (formed from pyruvic acid and *N*-aminoanabasine) is reduced with zinc in alcoholic hydrochloric acid, D-alanine is formed in an optical yield of 40%:



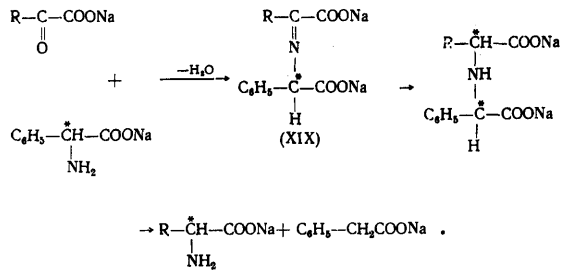
An exceptionally high optical yield was obtained by McCaully [51], who achieved a new synthesis from an optically active hydrazone-lactone (obtained from optically active 1-amino-2-hydroxymethylindoline and a ketoacid), the hydrolysis of which gives alanine (R = CH_3; p = 82%) and α-aminobutyric acid (R = C_2H_5, p = 98%), the initial 1-amino-2-hydroxymethylindoline being regenerated:



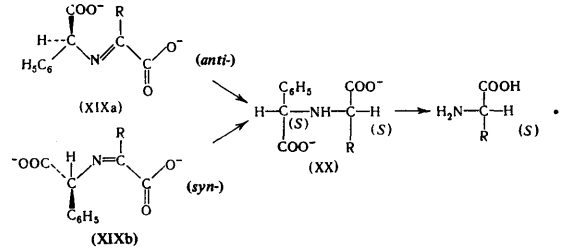
The high stereospecificity of the reaction in the stage involving the reduction by aluminium amalgam can be explained [52] by the *cis*-disposition of the five- and seven-membered rings in the molecule, which forces hydrogen to approach predominantly from one side.

Harada [53,54] employed as an asymmetrising agent optically active phenylglycine, the sodium salt of which was found to undergo readily hydrogenolysis on Pd/C at the C–N bond, giving ammonia and phenylacetic acid.

On the basis of this property, it proved possible to synthesise optically active alanine and α-aminobutyric, glutamic, and aspartic acids from the corresponding keto-acids and optically active phenylglycine according to the mechanism

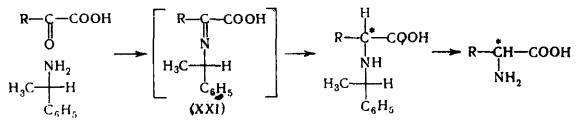


The asymmetric yield of α-aminoacids reaches 40 to 60%. To avoid an alteration of the optical yield during the isolation and purification of the product, measurements were made of the optical activities of the corresponding 2,4-dinitrophenyl derivatives of the aminoacids, which were separated chromatographically on Celite [55]. The mechanism proposed for this reaction consists in the asymmetric reduction of the intermediate Schiff base (XIX). Examination of the conformations of compound (XIX) led to the conclusion [53] that the hydrogenation of both possible isomers [the *syn*-isomer (XIXb) and the *anti*-isomer (XIXa)] leads to the same configuration of compound (XX):



According to this mechanism, the use of (*S*)-phenyl glycinate as the asymmetrising agent should give the aminoacid with the (*S*)-configuration and the use of (*R*)-phenylglycinate should give the corresponding (*R*)-amino acid. The results showed that these hypotheses are quite valid. It is interesting that the asymmetric yield changes little with increase in the size of the alkyl group at the α-carbon atom of ketoacids.

Hiskey and Northrop [56] obtained optically active amino-acids by hydrogenating the azomethine derivatives of α-ketoacids and (–)- and (+)-α-phenylethylamine on Pd/C, PtO_2, and $Pd(OH)_2/C$ catalysts according to the mechanism



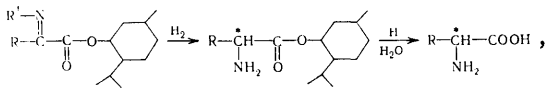
Compound (XXI) (a Schiff base) was not isolated or identified, being immediately subjected to catalytic hydrogenation and hydrogenolysis with formation of the amino-acid. The results of these experiments are presented in Table 6, which shows that the configuration of the amino-acid formed depends on that of the α-phenylethylamine employed: the (+)-amine promotes the formation of the D-aminoacid. The optical yield of the aminoacid varies

with the hydrogenation catalyst employed. The maximum optical yield was observed on 10% Pd/C. The addition of acid or alkali does not influence the course and the degree of asymmetric synthesis, in contrast to the asymmetric hydrogenation of ketoacids [22-24]. The size of the alkyl group in the α-ketoacid has a powerful influence on the degree of asymmetric synthesis. Thus, whereas the optical yield of D-alanine (R = CH_3) was 85%, under the same conditions phenylalanine (R = $C_6H_5CH_2$) was obtained with an optical yield of 56% and the optical yield of leucine [R = $(CH_3)_2CHCH_2$] was zero.

Table 6. Asymmetric yield of aminoacids obtained by the transamination of α-ketoacids RCOCOOH with optically active α-phenylethylamine.

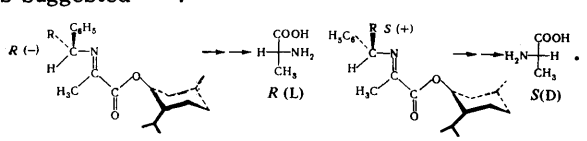
α-ketoacid, R	Catalyst	Configuration of amine	Yield of aminoacid, %	Configuration, sign of rotation, optical yield of aminoacid, %
CH_3	10% Pd/C	(+)	47.9	*D*, (−); 85.2
CH_3	10% Pd/C	(−)	43.1	*L*, (+); 90.7
CH_3CH_2	10% Pd/C	(−)	84.9	*L*, (+); 81.4
CH_3CH_2	$Pd(OH)_2/C$	(+)	71.7	*D*, (−); 71.7
CH_3CH_2	PtO_2	(+)	59.2	*D*, (−); 56.3
$(CH_3)_2CH$	10% Pd/C	(+)	15.7	*D*, (−); 64.2
$(CH_3)_3$	$Pd(OH)_2/C$	(+)	0.0	—
$C_6H_5CH_2$	10% Pd/C	(+)	53.8	*D*, (+); 56.4
$C_6H_5CH_2$	10% Pd/C	(−)	65.0	*L*, (−); 56.0

The asymmetric synthesis of aminoacids by the hydrogenation of the C=N bond was also investigated by Harada and Matsumoto [26,58]. The oximes of the (−)-menthyl esters of pyruvic, α-oxobutyric, and phenylglyoxylic acids and also the Schiff bases of these esters with benzylamine and optically active α-ethyl-α-methylbenzylamines were employed as the starting materials:



where R = CH_3, C_2H_5, or C_6H_5 and R′ = OH, $C_6H_5CH_2$, $C_6H_5CH(CH_3)$, or $C_6H_5CH(C_2H_5)$.

Table 7 shows that (−)-D-aminoacids are formed with a higher asymmetric yield in the hydrogenation of the oximes than in the hydrogenation of the corresponding Schiff bases with benzylamine. The stereochemistry of the reaction is consistent with Prelog's rule. On the other hand, the hydrogenation of Schiff bases with optically active amines showed that the asymmetric atom of the amine has a more marked influence on the stereospecific addition of hydrogen, namely when the (−)-(*R*)-amine was employed, the product was the (+)-L-aminoacid with a 19–24% optical yield. But when the steric effects of both asymmetric atoms are concerted, the yield of the amino-acid increases sharply and reaches 60%. Table 7 also shows that an increase in the size of the alkyl group at the asymmetric atom of the amine lowers the optical purity of the aminoacid formed. To account for these results, the following stereochemical reaction pathway was suggested [26,58]:



Kanai and Mitsui [59], who applied the method of Hiskey and Northrop [56,57], obtained optically active phenylglycine by the hydrogenation of benzoylformic acid and its ethyl ester in the presence of optically active (*S*)-phenylethyl-amine on various catalysts [PtO_2, Raney nickel, Pd/Cb, Pd/C_a, $Pd(OH)_2/C$]. It was established that the hydro-genation of ethyl benzoylformate on all the catalysts gives (*R*)-phenylglycine, while the hydrogenation of the acid itself under the same conditions leads to (*S*)-phenylglycine:

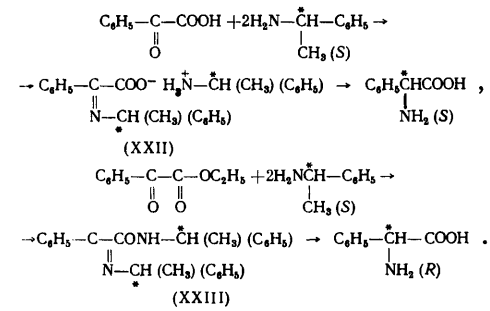
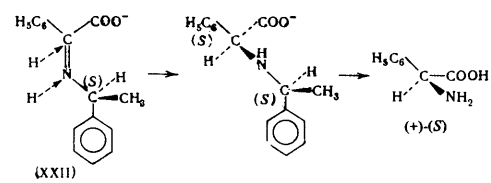


Table 7. Asymmetric synthesis of aminoacids by the hydrogenation of oximes and Schiff bases of (−)-menthyl esters of ketoacids.

R′ in initial compound	Catalyst	Yield, %	Optical purity of DNP-aminoacids*, %	Aminoacid
	(−)-Menthyl pyruvate			
OH	5% Pd/C	67	*D*-(−), 24.6	alanine
OH	$Pd(OH)_2/C$	70	*D*-(−), 24.5	ditto
$C_6H_5CH_2$	5% Pd/C	79	*DL*-(±), 0	»
$C_6H_5CH_2$	$Pd(OH)_2/C$	77	*D*-(−), 16.3	»
(−) $C_6H_5CH(CH_3)$	5% Pd/C	62	*L*-(±), 24.0	»
(−) $C_6H_5CH(CH_3)$	$Pd(OH)_2/C$	57	*L*-(+), 19.1	»
(−) $C_6H_5CH(C_2H_5)$	$Pd(OH)_2/C$	56	*S*-(+), 15	»
(+) $C_6H_5CH(CH_3)$	5% Pd/C	67	*D*-(−), 65.8	»
(+) $C_6H_5CH(CH_3)$	$Pd(OH)_2/C$	61	*D*-(−), 59.6	»
(+) $C_6H_5CH(C_2H_5)$	$Pd(OH)_2/C$	55	*R*-(−), 36	»
	(−)-Menthyl α-oxobutyrate			
$C_6H_5CH_2$	5% Pd/C	74	*DL*-(±), 0	α-aminobutyric acid
$C_6H_5CH_2$	$Pd(OH)_2/C$	69	*D*-(−), 7.6	ditto
OH	5% Pd/C	64	*D*-(−), 20.5	»
OH	$Pd(OH)_2/C$	62	*D*-(−), 20.7	»
	(−)-Menthyl phenylglyoxylate			
OH	5% Pd/C	88	*D*-(−), 49.1	phenylglycine
OH	$Pd(OH)_2/C$	84	*D*-(−), 44.2	ditto

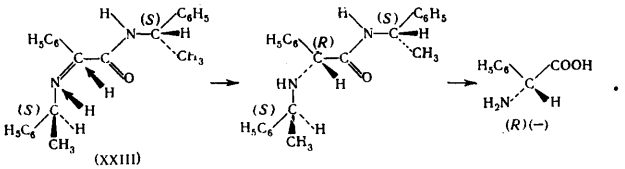
*DNP-aminoacid = dinitrophenyl derivative of aminoacid (Ed. of Translation).

The optical yield of phenylglycine did not exceed 2–3% with the exception of the hydrogenation of compound (XXII) on the highly stereospecific catalyst $Pd(OH)_2$, where the optical yield reached 73%. The authors suggested the following mechanism for the hydrogenation of compound (XXII):



To account for the experimental data, it is necessary to postulate that compound (XXIII) reacts preferentially

in the conformation where the imino- and amido-groups are in the *trans*-positions:



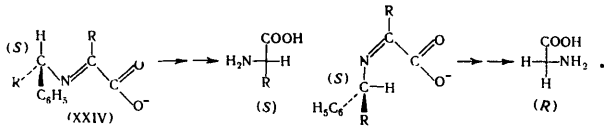
(XXIII)

An attempt was made [26] to investigate the mechanism of the asymmetric synthesis of α-aminoacids by the hydrogenation of the C=N bond. The hydrogenation was carried out on a $Pd(OH)_2/C$ catalyst at room temperature. Three types of reactions were investigated: (1) hydrogenation of the Schiff bases of α-ketoacids with (−)-(*S*)- and (+)-(*R*)-α-methylbenzylamines and (−)-(*S*)- and (+)-(*R*)-α-ethylbenzylamines; (2) hydrogenation of the oximes of (−)-(*S*)-*N*- and (+)-(*R*)-α-methylbenzylbenzoylformamide and (−)-(*S*)-*N*- and (+)-(*R*)-*N*-α-ethylbenzylbenzoylformamide; (3) hydrogenation of the Schiff bases of (−)-menthyl pyruvate with (−)-(*S*)- and (+)-(*R*)-α-methylbenzylamines and (−)-(*S*)- and (+)-(*R*)-α-ethylbenzylamines (Table 8); (4) hydrogenation of the Schiff bases of the isobutyl ester of pyruvoyl-(+)-(*S*)-alanine and the isobutyl esters of pyruvoyl-(+)-(*S*)- and -(−)-(*R*)-valines with benzylamine (Table 12).

Table 8. Hydrogenation of the Schiff bases of α-ketoacids and optically active α-methyl- and α-ethylbenzylamines.

Substrate R–C(=O)–COH, R=	Sign of rotation of α-R-benzylamine	Yield, %	Aminoacid: Configuration, sign of rotation	Aminoacid: Optical purity, %	DNP-aminoacid: Optical purity, %
CH_3	CH_3 (−)	78	*S*, (+)	63	67
	C_2H_5 (−)	76	*S*, (+)	52	52
	CH_3 (+)	76	*R*, (−)	77	65
	C_2H_5 (+)	72	*R*, (−)	39	51
C_2H_5	CH_3 (−)	72	*S*, (+)	37	39
	C_2H_5 (−)	69	*S*, (+)	36	33
	CH_3 (+)	70	*R*, (−)	38	37
	C_2H_5 (+)	68	*R*, (−)	39	36
C_6H_5	CH_3 (−)	73	*S*, (+)	28	30
	C_2H_5 (−)	70	*S*, (+)	25	24
	CH_3 (+)	73	*R*, (−)	29	31
	C_2H_5 (+)	69	*R*, (−)	24	26
$C_6H_5CH_2$	CH_3 (−)	73	*S*, (−)	12	14
	C_2H_5 (−)	70	*S*, (−)	5	10
	CH_3 (+)	71	*R*, (+)	13	14
	C_2H_5 (+)	71	*R*, (+)	5	11
CH_2CH_2COOH	CH_3 (−)	74	*S*, (+)	13	12
	C_2H_5 (−)	75	*S*, (+)	2	6

The reaction of type 1 was investigated to test the mechanism proposed by Kanai and Mitsui [59]. Table 8 shows that the optical purity of the aminoacids formed depends on the bulk of the alkyl group in the α-ketoacid; namely the optical purity falls in the series $CH_3 > C_2H_5 > C_6H_5 > > CH_2C_6H_5 > CH_2CH_2COOH$. The use of α-methylbenzylamine leads in all cases to a higher optical purity than is obtained with α-ethylbenzylamine. The data quoted contradict the mechanism proposed by Kanai and Mitsui [59]. If the conformations of molecules (XXII) and (XXIII) which they proposed are correct, the optical purity of the aminoacids should be independent of the size of the alkyl group and the optical yield should be higher when α-ethylbenzylamine is employed. Therefore it is necessary to put forward another mechanism for reactions of type 1:



(XXIV)

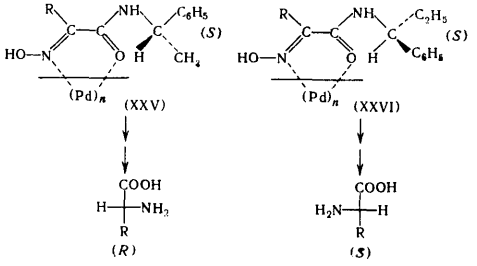
According to the experimental data, the structure (XXIV) is tentative but the increase in the size of the alkyl substituents both in the ketoacid and in the amine hinders the approach of hydrogen to the molecule, which lowers the optical purity of the product. This mechanism accounts satisfactorily for the experimental results and is consistent with the mechanism proposed by Hiskey and Northrop [56].

In reactions of type 2 optically active phenylglycine is obtained by the hydrogenation of the corresponding oxime. The results are given in Table 9.

Table 9. Hydrogenation of the oximes of optically active α-methyl- and α-ethyl-benzylbenzoylformamides.

Configuration of amine	Aminoacid: yield, %	Aminoacid: configuration, sign of rotation	Aminoacid: Optical purity, %	DNP-aminoacid: Optical purity, %
CH_3, (-)-(*S*)	56	*R*, (−)	1.5	5.5
C_2H_5, (-)-(*S*)	52	*S*, (+)	1.4	8.8
CH_3, (+)-(*R*)	53	*S*, (+)	0.8	4.9
C_2H_5, (+)-(*R*)	48	*R*, (−)	2.1	10.0

When (*S*)- or (*R*)-α-methylbenzylamines were employed, the products were (*R*)- and (*S*)-phenylglycines respectively, in agreement with Prelog's rule. However, the use of (*S*)- and (*R*)-α-ethylbenzylamines yielded (*S*)- and (*R*)-phenylglycines. To account for these results, it is necessary to postulate that both structures (XXV) and (XXVI) react in the cisoid conformation, as shown in the scheme below:



However, when the methyl group of the optically active amine is replaced by the ethyl group, the molecule should probably react more readily in conformation (XXVI) and give rise to the (*S*)-aminoacid. The carbonyl and azomethine groups can interact with the catalyst (Pd/C) forming coordinate bonds and giving rise to a five-membered cyclic complex. This stabilises the *cis*-conformation of the substrate molecule. The possibility of the formation of such complexes for compounds with C=O and C=N bonds was discussed by Hartung and coworkers [60].

The study of the hydrogenation of optically active azomethine derivatives in various solvents showed that an

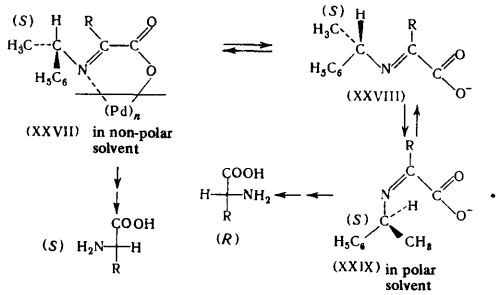
increase in the polarity of the solvent leads to a decrease of the optical density of the aminoacid formed (alanine, phenylalanine, phenylglycine) and even to a change in the sign of the rotation (glutamic acid) (Table 10) [29].

Table 10. Effect of solvents on the configuration and optical yields of aminoacids.

R—CO—COOR′	Configuration of amine, R in R − $\overset{*}{C}$H(NH)$_2$C$_6$H$_5$	Solvent	Aminoacid R—CHNH$_2$COOH		
			yield, %	configurational	optical purity*, %
R=CH$_3$ R′=H	(−)-(*S*)-CH$_3$	THF	33	(+)-(*S*)	66
		C$_2$H$_5$OH	78	(+)-(*S*)	67
		H$_2$O + pyridine	78	(+)-(*S*)	40
		NaOH + H$_2$O	69	(+)-(*S*)	33
	(−)-(*S*)-C$_2$H$_5$	C$_2$H$_5$OH	76	(+)-(*S*)	52
		C$_2$H$_5$OH + H$_2$O + NaOH	65	(+)-(*S*)	37
		CH$_3$OH:H$_2$O=1:4 +NaOH	75	(+)-(*S*)	31
	(+)-(*R*)-naphthyl	C$_2$H$_5$OH	76	(−)-(*R*)	83
		C$_2$H$_5$OH +H$_2$O+NaOH	65	(−)-(*R*)	73
R=CH$_3$ R′=CH$_2$C$_6$H$_5$	(−)-(*S*)-CH$_3$	hexane	75	(+)-(*S*)	72
		ethyl acetate	49	(+)-(*S*)	60
		isopropyl alcohol	56	(+)-(*S*)	46
		dimethylformamide	47	(+)-(*S*)	50
		CH$_3$OH	61	(+)-(*S*)	38
		dioxan: H$_2$O = 45:55	71	(+)-(*S*)	29
		CH$_3$OH:H$_2$O=2:1 **	75	(+)-(*S*)	35
		CH$_3$OH:H$_2$O=1:2 **	63	(+)-(*S*)	39
		CH$_3$OH:H$_2$O=1:4 **	76	(+)-(*S*)	29
		H$_2$O **	45	(+)-(*S*)	41
	(+)-(*R*)-CH3	dioxan	72	(−)-(*R*)	58
	(+)-(*R*)-C$_2$H$_5$	hexane**	66	(−)-(*R*)	74
	(+)-(*R*)-naphthyl	hexane**	31	(−)-(*R*)	86
		ethyl acetate	31	(−)-(*R*)	78
R=C$_6$H$_5$ R′=H	(−)-(*S*)-CH$_3$	C$_2$H$_5$OH	73	(+)-(*S*)	30
		H$_2$O + NaOH	60	(+)-(*S*)	24
R=CH$_2$COOH, R′=H	(−)-(*S*)-CH$_3$	C$_2$H$_5$OH + H$_2$O + NaOH	38	(+)-(*S*)	58
			11	(−)-(*R*)	45
R=(CH$_2$)$_2$COOH R′=H	(−)-(*S*)-CH$_3$	isopropyl alcohol + triethylamine	82	(+)-(*S*)	14
		C$_2$H$_5$OH	74	(+)-(*S*)	12
		CH$_3$OH + triethylamine	78	(+)-(*S*)	5
		dioxan:H$_2$O = 2:8 + triethylamine	60	(−)-(*R*)	19
		CH$_3$OH:H$_2$O=1:2 +NaOH	68	(−)-(*R*)	27
		H$_2$O + pyridine	55	(−)-(*R*)	27
	(+)-(*R*)-C$_2$H$_5$	C$_2$H$_5$OH	75	(−)-(*R*)	6
	(−)-(*S*)-C$_2$H$_5$	H$_2$O:CH$_3$OH=2:1 + NaOH	56	(−)-(*R*)	30

*The optical purity was calculated from the optical rotation of the dinitrophenyl derivatives of the aminoacids.
**The reaction mixture was not homogeneous.

The results suggest that the reactive conformation of the molecule changes under the influence of the solvent according to the mechanism



In a non-polar solvent the structure (XXVII) is more favourable, since the electrostatic attraction between the catalyst and the substrate is greater than under conditions where polar solvents are employed; the weak solvation of the substrate molecules in non-polar solvents promotes a more ready formation of the intermediate complex with the catalyst. In polar solvents the non-chelate structure (XXIX), which can be converted into the non-chelate structure (XXVIII) with decrease of the polarity of the medium, is more likely.

A study of the hydrogenation of oxaloacetic acid in the presence of various amines was undertaken to obtain optically active aspartic acid [61]. It was found that, depending on the amine and the solvent employed, either a mixture of alanine and aspartic acid or alanine alone are obtained (Table 11). The hydrogenation of the Schiff base with benzylamine in alcoholic solution gives racemic alanine. A similar result is also obtained with optically active α-methyl- and α-ethyl-benzylamines. On the other hand, when (+)-(*S*)- and (−)-(*R*)-phenylglycines were used, mixtures of (+)-(*S*)-alanine and (+)-(*S*)-aspartic acid and of (−)-(*R*)-alanine and (−)-(*R*)-aspartic acid were obtained:

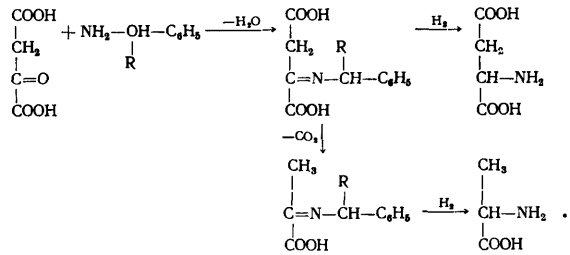


Table 11. The formation of optically active alanine and aspartic acid from oxaloacetic acid and α-alkylbenzylamines.

Configuration of amine	Solvent	Yield, %	Configuration of aminoacid	Optical yield of DNPh-aminoacid, %
(−)-(*S*)-CH$_3$	C$_2$H$_5$OH	78	(+)-(*S*)-alanine	69
(−)-(*S*)-CH$_3$	H$_2$O, C$_2$H$_5$OH (1:1) + NaOH	60	(+)-(*S*)-alanine	51
			(−)-(*R*)-aspartic acid	45
(−)-(*S*)-C$_2$H$_5$	C$_2$H$_5$OH	75	(+)-(*S*)-alanine	52
(−)-(*S*)-C$_2$H$_5$	H$_2$O, C$_2$H$_5$OH (1:1) + NaOH	56	(+)-(*S*)-alanine	37
			(−)-(*R*)-aspartic acid	25
(+)-(*R*)-naphthyl	C$_2$H$_5$OH	75	(−)-(*R*)-alanine	83
(+)-(*R*)-naphthyl	H$_2$O, C$_2$H$_5$OH (1:1) + NaOH	65	(−)-(*R*)-alanine	73
(+)-(*S*)-COOH	H$_2$O, NaOH	40	(+)-(*S*)-alanine	60
			(+)-(*S*)-aspartic acid	53
(−)-(*R*)-COOH	H$_2$O, NaOH	38	(−)-(*R*)-alanine	62
			(−)-(*R*)-aspartic acid	53

The above reaction mechanism presupposes that the Schiff base of oxaloacetic acid formed can be readily decarboxylated with formation of the corresponding Schiff base of pyruvic acid, the hydrogenation and subsequent hydrogenolysis of which give alanine.

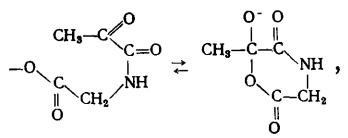
The mechanism of the asymmetric hydrogenation of azomethine derivatives of α-ketoacids proposed above [26] consists in the formation of an intermediate complex (XXV, (XXVI) of the compound with the Pd catalyst and the subsequent adsorption of the substrate molecule on the catalyst surface and the addition of hydrogen to the C=N bond. This mechanism is proved by the results of an investigation of similar reactions in media of different polarity [29] and also the study of asymmetric hydrogenation of compounds with a peptide bond [57,62]. Hiskey and Northrop [57] achieved the asymmetric synthesis of peptides in the following experiments:

(a) reduction of *N*-pyruvoylglycine with optically active α-methylbenzylamine;

(b) reduction of *N*-pyruvoyl-L-alanine with optically active α-methylbenzylamine;

(c) reduction of *N*-pyruvoyl-L-alanine with benzylamine.

The experimental results showed that in the hydrogenation of the Schiff bases of pyruvoylglycine with (−)- and (+)-α-methylbenzylamines the optical yield of alanylglycine (30–60%) is lower than in the reduction of pyruvic acid under the same conditions (cf. Table 6). This can be accounted for by the unfavourable interaction between the keto- and carboxy-groups,

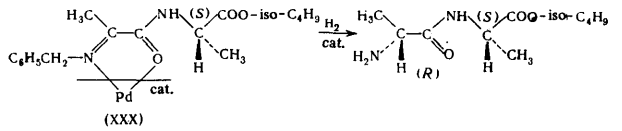


and also by an increase of steric hindrance due to the bulky substituent (glycine) at the carboxy-group of the ketoacid. Steric correlations in accordance with Prelog's rule hold in the reaction: when the (−)-amine is employed, the L-peptide is obtained and the (+)-amine gives rise to the D-peptide. The hydrogenation of *N*-pyruvoyl-L-alanine under the same conditions showed that the asymmetric atom of L-alanine does not play the main role in the formation of the new asymmetric centre: when the D-amine was employed, the product contained an excess of the D-L-isomer of the dipeptide, while in the presence of the L-amine, the L-L-isomer was obtained in excess. The hydrogenation of *N*-pyruvoyl-L-alanine in the presence of optically inactive benzylamine was carried out to elucidate the asymmetrising effect of the L-alanyl part of the molecule. Contrary to expectation, the D-L-dipeptide was found to be in an excess, although Prelog's rule predicts the formation of the L-L-dipeptide.

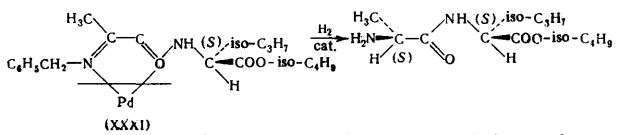
It is noteworthy that the dipeptides were obtained in these reactions in low yields (up to 30%). Possibly this is because *N*-pyruvoylalanine is reduced to lactic acid at a higher rate than that of the formation of the Schiff base; indeed lactic acid was found in the reaction mixture in a yield greater than 80%.

Harada and Matsumoto [62] achieved similarly the asymmetric synthesis of certain alanyl dipeptides and found that, in the hydrogenation of the Schiff bases of the isobutyl and methyl esters of *N*-pyruvoyl-(*S*)-alanine with benzylamine, the newly formed asymmetric atom has the (*R*)-configuration, i.e. the results are consistent with those of Hiskey and Northrop [57]. But, when the esters of optically active valine, leucine, phenylalanine, phenylglycine, and aspartic and α-aminobutyric acids were employed as the asymmetrising agents, the (*S*,*S*)-alanyl dipeptide was formed preferentially.

The authors proposed the following stereochemical mechanism for the reaction:



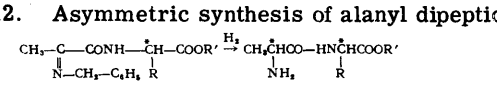
(XXX)



(XXXI)

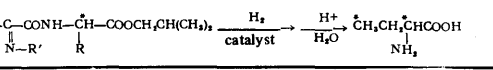
When the alkyl substituent at the asymmetric carbon atom is R = CH_3, the substrate molecule reacts preferentially in conformation (XXX), but when the R group is larger than methyl, in all other reactions hydrogenation takes place preferentially with the substrate in conformation (XXXI). In both conformation (XXX) and (XXXI) the C=N and C=O groups are in the *cis*-positions stabilised by the formation of a complex with the catalyst. If the asymmetrising agent has the (*S*)-configuration, the hydrogenation of the molecule in conformation (XXX) leads to the formation of (*R*)-alanine, while conformation (XXXI) induces the formation of (*S*)-alanine. The hydrogenation of the Schiff bases and oximes of α-oxobutyric acid activated by various optically active aminoacids showed that in this case the reaction takes place preferentially in conformation (XXXI) (Table 13).

Table 12. Asymmetric synthesis of alanyl dipeptides



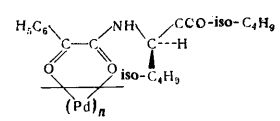
Asymmetrising agent			Configuration of alanine formed, optical yield, %
R	R′	Configuration	
CH_3	$CH_2CH(CH_3)_2$	*S*	*R*, 64
CH_3	CH_3	*S*	*R*, 52
C_6H_5	$CH_2CH(CH_3)_2$	*S*	*S*, 41
$(CH_3)_2CH$	$CH_2CH(CH_3)_2$	*S*	*S*, 32
$(CH_3)_2CH$	$CH_2CH(CH_3)_2$	*R*	*R*, 32
$(CH_3)_2CH$	CH_3	*S*	*S*, 17
$(CH_3)_2CHCH_2$	$CH_2CH(CH_3)_2$	*S*	*S*, 35
$(CH_3)_2CHCH_2$	CH_3	*S*	*S*, 18
$C_6H_5CH_2$	$CH_2CH(CH_3)_2$	*S*′	*S*, 25
$(CH_3)_2CHCH_2OOCCH_2$	$CH_2CH(CH_3)_2$	*S*	*S*, 25
C_6H_5	$CH_2CH(CH_3)_2$	*R*	0

Table 13. Asymmetric synthesis of α-aminobutyric acid.



Asymmetrising agent			Configuration of α-aminobutyric acid formed, optical yield, %
R	R′	Configuration	
C_6H_5	OH	*R*	0
$C_6H_5CH_2$	$CH_2C_6H_5$	*S*	*S*, 12
$C_6H_5CH_2$	OH	*S*	*S*, 9
$(CH_3)_2CHCH_2OOCCH_2$	$CH_2C_6H_5$	*S*	*S*, 28

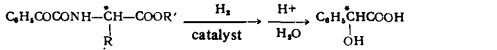
That the reaction proceeds via the formation of a complex of the substrate with the catalyst is proved to some extent by the study of the asymmetric synthesis of mandelic acid [62] (Table 14). Assuming that the molecule (for example in the synthesis of mandelic acid) forms with the catalyst a complex via two C=O bonds,



the authors concluded that the steric hindrance in the adsorption of keto-compounds is lower than for the azomethine derivatives (oximes and Schiff bases). The substituent at the C=N bond in the azomethines (OH or $CH_2C_6H_5$) increases the steric hindrance between the substrate and the catalyst and therefore the use of (*S*)-alanine alone (R = CH_3) leads to the (*R*)-configuration of the new asymmetric atom, i.e. the molecule reacts in

conformation (XXX). In the hydrogenation of the keto-group the use of esters of (*S*)-alanine (R = CH_3) and (*S*)-leucine [R = $(CH_3)_2CHCH_2$] yields (*R*)-mandelic acid and only the use of (*S*)-valine [R = $(CH_3)_2CH$] gives rise to (*S*)-mandelic acid. Consequently in the first two reactions the substrate molecule reacts in conformation (XXX) and in the last case the preferred conformation is (XXXI).

Table 14. Asymmetric synthesis of mandelic acid



Asymmetrising agent			Configuration of mandelic acid, optical yield, %
R	R′	Configuration	
CH_3	CH_3	*S*	*R*, 3
CH_3	$CH_2CH(CH_3)_2$	*S*	*R*, 14
CH_3	$CH_2CH(CH_3)_2$	*R*	*S*, 13
$(CH_3)_2CHCH_2$	$CH_2CH(CH_3)_2$	*S*	*R*, 11
$(CH_3)_2CH$	$CH_2CH(CH_3)_2$	*S*	*S*, 2

The numerous examples quoted above demonstrate a significant effect of the substituent at the reacting bond on the effectiveness of asymmetric catalysis. Formally this phenomenon may be described by the correlation equation derived by Ugi [63] for asymmetric hydrogenation, which is of the form

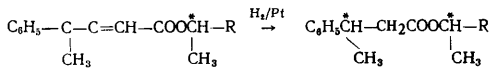
$$\lg Sp = \lg \frac{p}{100 - p} = \varkappa\tau\delta_p,$$

where κ is the "chirality parameter" determined from $\kappa = (\lambda_1 - \lambda_2)(\lambda_2 - \lambda_3)(\lambda_3 - \lambda_1)$ (λ_1, λ_2, and λ_3 are constants characterising the groups linked to the asymmetric atom in the ligands) and τ and δ_p are empirical constants.

Table 15. Calculation of the stereospecificities *Sp* from Ugi's equation for the hydrogenation of β-methylcinnamic acid esters.

R	$\varkappa$	δ_p	*Sp* (for $\tau = 0.110$)		λ_R constant for group R
			calc.	found	
$(CH_3)_3C$	−0.730	−1	54.6	54.3	1.49
C_6H_5	−0.283	−1	52.0	52.3	1.23
$2,4,6\text{-}(CH_3)_3C_6H_2$	0.918	1	55.8	56.5	1.58
$1\text{-}C_{10}H_7$	−0.375	−1	52.5	53.8	1.29
$2,4,6\text{-}(C_6H_{11})_3C_6H_2$	2.303	1	64.3	63.5	2.10

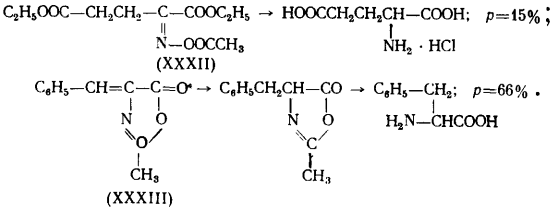
For the hydrogenation of a number of optically active esters of β-methylcinnamic acid in acetic acid on platinum at 20°C, the calculated values of *Sp* agree well with experiment (Table 15).



IV. CATALYTIC SYNTHESIS OF OPTICALLY ACTIVE AMINOACIDS ON DISSYMMETRIC CATALYSTS

The first unsuccessful attempts at the asymmetric hydrogenation of acetophenone on nickel in the presence of cholic acid or sodium deoxychelate may be regarded as attempts at modifying the catalyst surface by adding an optically active compound to produce a dissymmetric catalyst [64]. Thus the asymmetric reduction by hydrogen transfer [36-38] could also be interpreted as involving interaction to some extent between the hydrogen donor (glucose) and the surface of the metal catalyst whereby the latter is specifically modified.

Isoda and coworkers [65] showed for the first time that the catalyst obtained by the reduction of the Pd–L-tyrosine complex is capable of promoting the asymmetric hydrogenation of compounds (XXXII) and (XXXIII) with formation of (−)-D-glutamic acid and (+)-D-phenylalanine:

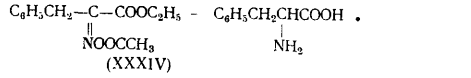


(XXXII)

(XXXIII)

Partial optical activation of the aminoacids formed is observed also in the hydrogenation of compounds (XXXII) and (XXXIII) on Raney nickel treated with (−)-tyrosine, (−)-leucine, (−)-phenylalanine, or (−)-arginine. Treatment with (−)-methionine does not lead to optically active products. At the same time modification of the Pd/C catalyst with methionine can be achieved and the hydrogenation of α-acetamidocinnamic acid (XXXIV) on such a catalyst leads to the formation of L-phenylalanine [66].

Isoda and coworkers [65] were guided by the statements of Akabori and coworkers [67-99], who obtained a dissymmetric catalyst by reducing $PdCl_2$ (33 wt.%) deposited on silk fibres at 50°C and 80 atm. In their first communications, Akabori and coworkers stated that such a catalyst is capable of promoting the asymmetric synthesis of aminoacids by the hydrogenation of (XXXII), (XXXIII), and (XXXIV) with an appreciable asymmetric yield—39, 38, and 26% respectively:

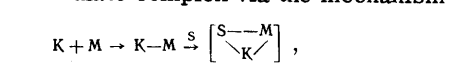


(XXXIV)

However, it is difficult to reproduce these results [70,71]. The studies of the effect of disymmetric nickel catalysts modified by optically active compounds were developed further in a number of investigations by Izumi, Akabori, and coworkers [70-73], mainly in the hydrogenation of the carbonyl group on the catalyst modified with (+)-tartaric acid [74] and aminoacids.

Klabunovskii and Petrov [75,76] extended the study of modified nickel catalysts to the hydrogenation of the C=N bond. Thus the hydrogenation of acetophenoxime takes place asymmetrically ($p = 2.6\%$), which suggests that there is a possibility of the application of these catalysts in the synthesis of optically active aminoacids. This method has an undoubted advantage over others, since there is no need to introduce an asymmetrising group into the initial molecule.

There are so far few data on the mechanism of the asymmetrising effect of modified catalysts but already certain conclusions may be made [75,77]. Probably asymmetric hydrogenation takes place only with formation of a fairly stable intermediate complex via the mechanism



where S is the substrate, M the optically active modifying agent, and K the catalyst.

The formation of such a complex fixes the conformation of the reacting molecule in a particular way. The M–K, K–S, and S–M interactions in the complex may be examined in succession.

The M–K bond is responsible for the modification of the catalyst and the formation of a surface nickel complex with the modifying substance (hydroxy- or amino-compound). Such complexes are centres for asymmetric hydrogenation and the maximum asymmetric effect will be observed for the optimum stability of the complex. Approximate data on the stability of the M–K bond may be obtained from the stability constants K_S of nickel complexes of hydroxy- or amino-acids. Comparison of the literature data for the stability constants of the nickel complexes of certain aminoacids and the stereospecificities Sp shows that Sp passes through a maximum as K_S increases, i.e. an unduly high stability of the complex has an unfavourable effect on asymmetric catalysis—a situation analogous to the energy correspondence (the equality of the adsorption potential of the optimum catalyst to half the sum of the energies of the reacting bonds in the molecule) considered in the multiplet theory of catalysis. Klabunovskii showed [77] that there is an approximately linear relation between the logarithm of the stereospecificity Sp and the change in the enthalpy ΔH of the catalyst modifying agent employed in the hydrogenation of methyl acetoacetate on nickel modified with tartaric, malic, and mandelic acids, alanine, and leucine:

$$RT \ln Sp \simeq \Delta H .$$

The K–S bond is altered under the influence of the modification of the catalyst and therefore the bonding energy Q between the atoms in the reacting molecule and the catalyst Q_{K-S} will differ from the value $Q_{K'-S}$ for the unmodified catalyst K′.

The experimental data [70-73,78-80] show that, since fairly stable complexes are formed on chemisorption of C=O, C–OH, and C=N groups in the reacting molecule, the asymmetrising property of the catalyst is shown only in relation to C=O and C=N but not C=C bonds.

It is so far difficult to make a quantitative assessment of the S–M bond and therefore the only measure of the interaction between the molecules of the substrate and the modifying agent is the stereospecificity of the reaction.

Qualitative data may be obtained about the nature of the K–S and K–M bonds by means of the energy calculations of the multiplet theory of catalysis. The energies of the bonds of nickel with oxygen and nitrogen (57.7 and 29.3 kcal) greatly exceed the values for palladium and platinum (44.1 and 25.1 kcal; 34.3 and 24.4 kcal) and therefore nickel is readily modified by compounds containing free amino- and hydroxy-groups and forms more readily reactive complexes with substrates containing C=O and C=N bonds. At the same time the energy of the bond with hydrogen decreases in the series $Q_{Pt-H} > Q_{Pd-H} > Q_{Ni-H}$, which facilitates the adsorption of the reacting compound on nickel and the oriented adsorption of the substrate molecule becomes rate-limiting.

However, these theoretical concepts still require a detailed experimental and quantitative development.

The validity of the hypothesis that asymmetric catalysis takes place via the formation of intermediate complexes is apparently confirmed by the known cases of the asymmetric synthesis of aminoacids [81,82] and asymmetric reactions under the influence of disymmetric catalysts [83-87].

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