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Advances in the Asymmetric Synthesis of α-Amino-acids

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The review deals with the advances in the asymmetric synthesis of α-amino-acids. Depending on the nature of the asymmetric reactions, the subject matter has been divided into two parts: asymmetric synthesis of α-amino-acids by catalytic hydrogenation and condensation methods of asymmetric synthesis. The principal characteristics of the asyymetric syntheses have been assessed as a function of various factors: the type of catalyst, the structure of the substrates, and the solvent. Much attention has been devoted to theoretical concepts which make it possible to understand the reasons for the occurrence of a new dissymmetric centre and the dependence of its configuration on that of the asymmetrising agent. The bibliography includes 85 references.

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I. INTRODUCTION

The requirement for α-amino-acids is at present very great: their use in biochemistry, food, medicine, etc. is being extended. A number of effective synthetic and microbiological methods have been developed for the preparation of α-amino-acids both on laboratory and industrial scales [1,2]. A disadvantage of the synthetic methods is the formation of optically inactive racemic products. Therefore, despite the existence of many methods for the separation of racemic α-amino-acids into optical isomers [1], synthesis has acquired increasing importance, particularly in recent times [3-5].

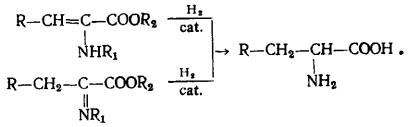
The essential feature of the asymmetric synthesis consists in the generation in the molecule during the reaction under the influence of asymmetrising agents of a new dissymmetric centre with a definite steric configuration. If the asymmetrising agent is an optically active compound, usually eliminated after the formation of the new dissymmetric centre, we are dealing with partial asymmetric synthesis. When a physical asymmetrising factor is employed, for example circularly polarised light, we are dealing with absolute asymmetric synthesis.

While the first successful asymmetric syntheses were achieved as early as the beginning of the present century, the asymmetric synthesis of α-amino-acids began to be investigated systematically only in the last decade. Klabunovskii's monograph [3] published in 1960 described the asymmetric synthesis of α-amino-acids only in general terms, since the bulk of the work on this question was published after 1960. Isolated examples of the asymmetric synthesis of α-amino-acids can be found in books [4,5] dealing with problems of the stereochemistry of organic compounds. These data are supplemented to some extent by the reviews of Mitsui dealing with asymmetric synthesis [6] and asymmetric hydrogenation [7].

In the present paper studies on the asymmetric synthesis of α-amino-acids published up to 1968 are reviewed. In the assessment of the results of asymmetric synthesis the authors endeavoured as far as possible to describe its principal characteristic: the yield of the main product and its optical purity or degree of asymmetric synthesis. Much attention has been devoted to theoretical concepts which explain the relation between the configurations of the new dissymmetric centre and the asymmetrising agent.

II. ASYMMETRIC HYDROGENATION OF DOUBLE BONDS

One of the main methods for the asymmetric synthesis of α-amino-acids is the asymmetric hydrogenation of their unsaturated precursors. This group of compounds includes αβ-unsaturated α-amino-acids and the imino-derivatives of α-keto-acids:



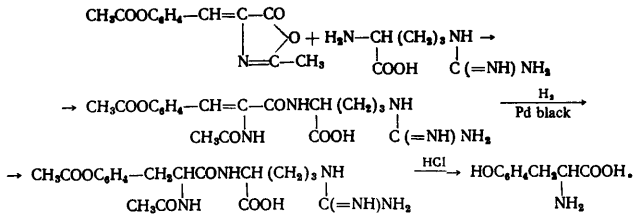
The asymmetric hydrogenation of double bonds results in the formation of an asymmetric α-carbon atom. After the elimination of the groups R_1 and R_2, optically active α-amino-acids are obtained.

The asymmetrising agent in catalytic hydrogenation may be the optically active group R_1 or R_2 forming part of the initial molecule and eliminated after asymmetric hydrogenation or a dissymmetric catalyst may be used. In the latter case the initial molecule does not contain optically active groups.

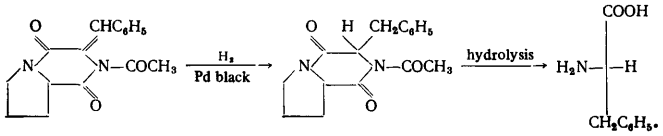
1. Asymmetric Hydrogenation of αβ-Unsaturated α-Amino-acids

The first asymmetric synthesis of an α-amino-acid by catalytic asymmetric hydrogenation was that of D-tyrosine

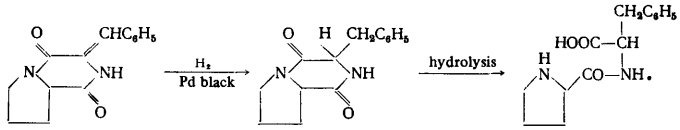
achieved by Bergmann et al.[8] L-Arginine was used as the asymmetrising agent. The hydrogenation over palladium black of the unsaturated peptide of α-acetamido-*p*-acetoxycinnamic acid and L-arginine resulted in the preferential formation of diacetyl-D-tyrosyl-L-arginine. The hydrolysis of the dipeptide in 20% hydrochloric acid yielded D-tyrosine with $[\alpha]_D^{21} = +9.5°$ (4% HCl); for optically pure D-tyrosine, $[\alpha]_D^{20} = +11.8°$:



Somewhat later Bergmann and Tietzmann[9] obtained the dioxopiperazine derivative of *N*-acetyl-L-phenylalanyl-L-proline with $[\alpha]_D^{22} = +202.6°$ in about 50% yield by the reduction of the optically active dioxopiperazine derivative of *N*-acetyldehydrophenylalanyl-L-proline over palladium black. After the hydrolytic elimination of the asymmetrising agent (L-proline), L-phenylalanine with $[\alpha]_D^{27} = -33.9°$ was obtained:

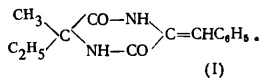


After the hydrogenation of the dioxopiperazine derivative of dehydrophenylalanyl-L-proline over palladium black, the dioxopiperazine derivative of L-phenylalanyl-L-proline was isolated, its hydrolysis in hydrochloric acid giving a 25% yield of pure L-prolyl-L-phenylalanine with $[\alpha]_D^{25} = -40.8°$ (5% in 20% HCl):



Although the initial asymmetrising agent (L-proline) was contained in the resulting dipeptide, nevertheless it can be supposed that L-phenylalanine is formed preferentially during the hydrogenation, since the rotation of the peptide agreed satisfactorily with that of synthetic L-prolyl-L-phenylalanine ($[\alpha]_D^{20} = -40.9$).[10]

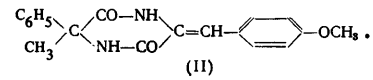
Subsequently, using optically active α-amino-acids as the asymmetrising agents, Akabori and coworkers[11,12] achieved the asymmetric synthesis of phenylalanine. They obtained from the methyl ester of *N*-chloroacetyl-L-isovaline acted upon by ammonia in methanol the dioxopiperazine derived from glycyl-L-isovaline, which in the presence of acetic anhydride at 160°C forms with benzaldehyde the dioxopiperazine derived from dehydrophenylalanyl-L-isovaline (I). Hydrogenation of compound (I) over platinum oxide yields the dioxopiperazine derived from L-phenylalanyl-L-isovaline, from which L-phenylalanine with $[\alpha]_D^{12} = -29°$ was obtained after the hydrolytic elimination of the asymmetrising agent—L-isovaline:



(I)

The corresponding D-compounds were obtained similarly from *N*-chloroacetyl-D-isovaline.

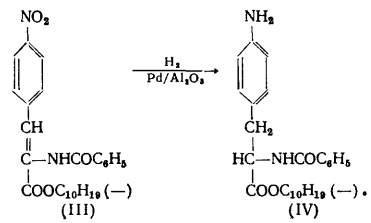
Using the same sequence of reactions, Maeda[13] synthesised optically active L-tyrosine with $[\alpha]_D^{20} = -2.14°$ (20% HCl) by the catalytic hydrogenation over palladium oxide of compound (II) with subsequent hydrolysis of the resulting dioxopiperazine:



(II)

In this case the starting compound and the asymmetrising agent was *N*-chloroacetyl-(+)-α-amino-α-phenylpropionic acid.

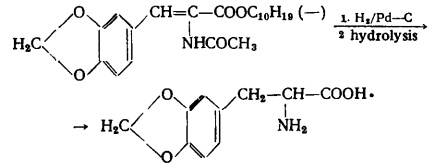
Together with optically active amino-acids, optically active menthol has found wide application as an asymmetrising agent. In the hydrogenation of (−)-menthyl esters of α-benzamido-*p*-nitrocinnamic acid (III) over palladium deposited on alumina, Pedrazzoli[14,15] obtained at 60°C a mixture of two diastereoisomeric (−)-menthyl esters of *p*-amino-α-benzamidohydrocinnamic acid containing 30% of the ester (IVa) with $[\alpha]_D = -9°$ (0.5; alcohol) and 60% of the ester (IVb) with $[\alpha]_D = -47.5°$ (0.5; alcohol). After fractional crystallisation, the esters (IVa) and (IVb) were hydrolysed and virtually optically pure D-*p*-aminophenylalanine [from compound (IVa)] with $[\alpha]_D = +45°$ (1.5; water) and L-*p*-aminophenylalanine [from compound (IVb)] with $[\alpha]_D = -42°$ (1.5; water) were obtained:



(III) (IV)

In order to estimate the degree of asymmetric synthesis achieved in the stage involving the hydrogenation of the ester (III), it is necessary to take into account the relative amounts of the diastereoisomers (IVa) and (IVa). Since the amount of compound (IVb) formed was twice as great as that of compound (IVa), the degree of asymmetric synthesis or the optical yield of the reaction amounts to about 33%. The hydrogenation under the same conditions of the bornyl ester of α-benzamido-*p*-nitrocinnamic acid yielded after one recrystallisation from benzene and subsequent acid hydrolysis virtually inactive *p*-aminophenylalanine with $[\alpha]_D^{25} = +2°$ (1.5; water).

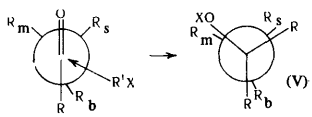
In some cases the isolation of the racemic final product does not alone constitute evidence of the absence of asymmetric synthesis. The isolation of certain α-amino-acids from their derivatives may be accompanied by racemisation. However, if unequal amounts of the diastereoisomers are formed in the hydrogenation stage, asymmetric synthesis still takes place. Thus Yamada et al.[16], who reduced the (−)-menthyl ester of α-acetamido-β-[3,4-methylenedioxyphenyl]acrylic acid in the presence of 10% palladium on charcoal in ethanol and benzene, obtained an excess of the laevorotatory hydrogenation product—an L-alanine derivative, the excess being greater in ethanol than in benzene:



However, both acid and alkaline hydrolysis of the ester was accompanied by almost total racemisation, as a result of which optically inactive 3,4-methylenedioxyphenylalanine was isolated.

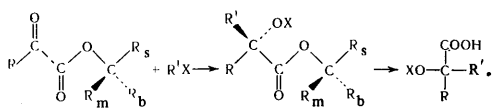
Recently the study of asymmetric syntheses has been based on theoretical concepts whereby it is possible to predict the configuration of the optical isomer formed preferentially. The studies of Cram [17] and Prelog and coworkers [18-21] are important in the development of such concepts, based on the examination of the conformation of molecules.

The investigation of the addition of various reagents, for example hydride hydrogen or organometallic compounds, to the carbonyl group adjacent to the dissymmetric centre, enabled Cram and Abd Elhafez [17] to establish a relation whereby it is possible to predict the configuration of the diastereoisomer formed. The starting material reacts with the reagent R'X in the conformation where the carbonyl oxygen is located between the two smallest substituents and the dissymmetric centre (R_S, R_m, and R_b are small, medium, and big substituents respectively).



The reagent R'X approaches the carbonyl oxygen from the sterically less hindered side, i.e. from the side of the group R_S, which leads to the preferential formation of the compound with the configuration (V). In this case it is possible to observe the maximum influence of the asymmetrising agent, since the centre inducing the asymmetry is directly linked to the dissymmetric centre produced.

Prelog and coworkers [18-21] showed that similar concepts may be used also for systems in which the asymmetrising centre is not located in the immediate vicinity of the dissymmetric centre produced. Thus Prelog examined the stereochemical specificity of the reaction of the α-keto-esters of asymmetric alcohols with Grignard reagents:

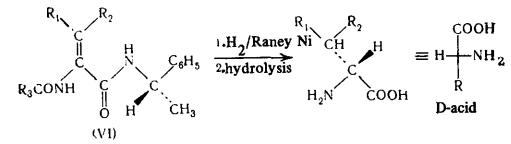


In Prelog's mechanism the α-keto-ester molecule is arbitrarily oriented in such a way that both carbonyl groups are *antiparallel* and the *smallest* group R_S of the optically active residue of the alcohol is in the plane of the ester group. Then the reagent R' approaches the ketonic carbonyl group from the side of the medium-size substituent R_m which in fact determines the preferential configuration of the reaction product formed. The reagent can also of course approach the reaction centre from the other, more sterically hindered side, which lowers the optical purity of the product.

Since the reaction products are diastereoisomeric, it may be assumed that the transition states leading to them are also diastereoisomeric and consequently differ in free energy. However, since the initial state in both cases is the same, the activation energies for these reactions are different and the two products are formed at different rates.

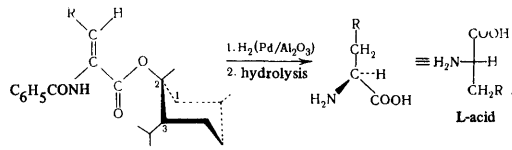
Similar ideas can be used also in the study of catalytic asymmetric reactions [20,21]. However, in contrast to homogeneous catalytic syntheses, in asymmetric syntheses in the presence of heterogeneous catalysts such simple relations may be complicated by the orienting effect of the catalyst surface [22].

Using the concepts of Cram and Prelog, Sheehan and Chandler [23] were able to predict the configuration of the valine and phenylalanine isomers formed in excess in the hydrogenation of the corresponding optically active methylbenzylamides of α-acetamido-αβ-unsaturated acids over Raney nickel. L-(−)-α-Methylbenzylamine, the L-configuration of which had been established by Leite [24] on the basis of its relation to that of L-alanine, was used as the asymmetrising agent. It was assumed that hydrogen is adsorbed on the surface of the catalyst and that the substrate reaches the catalytic surface from the least hindered side. When L-(−)-α-methylbenzylamine is used, the least hindered side for the substrate (V) will be the region over the plane of the image and consequently the α-amino-acid formed will have the D-configuration.



Indeed, in the hydrogenation of L-α-methylbenzylamide of α-acetamido-ββ-dimethylacrylic acid ($R_1 = R_2 = R_3 = CH_3$) followed by the acid hydrolysis of the hydrogenation product, D-valine of 39% optical purity was obtained in 90% yield. The hydrogenation of the corresponding benzoyl derivative ($R_3 = C_6H_5$) also resulted in the formation of D-valine of 18% optical purity in 90% yield. On the other hand, when the D-α-methylbenzylamide of α-benzamido-ββ-dimethylacrylic acid ($R_1 = R_2 = CH_3$; $R_3 = C_6H_5$; asymmetrising agent—D-α-methylbenzylamine) was hydrogenated, the final product was L-valine of 18% optical purity. D-Phenylalanine with an optical yield of 6% (reaction yield 91%) was obtained similarly from L-α-methylbenzylamide of α-benzamidocinnamic acid ($R_1 = R_3 = C_6H_5$; $R_2 = H$).

The preferential formation of L-*p*-aminophenylalanine observed by Pedrazzolli [14,15] can be explained similarly:



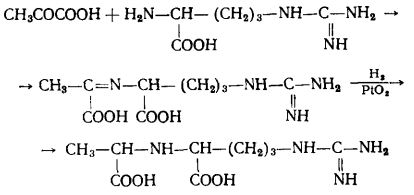
According to Prelog, the (−)-menthyl residue is oriented in such a way that the smallest substituent at the C_2–H atom is screened by the double bond. Of the other two substituents at the C_2 atom, the methylene group of the ring (at C_1) may be regarded as of medium size and the methylidyne group with an isopropyl substituent (C_3) may be regarded as having the maximum size. Consequently hydrogen will attack the double bond preferentially from the least hindered side of the methylene group of the ring (C_1), i.e. from the side opposite to that of the plane of the image. Hence it is clear that an α-amino-acid with the L-configuration should form preferentially.

However, one should bear in mind the possible distortion of the relative amounts of the stereoisomers in the isolation of the reaction product. Therefore in the estimation of the optical yield one should not consider the yield of the optically active substance after isolation but its formation as a result of the reaction. Since in a number of studies [8,9,11-13] the yield of the main reaction product did not exceed 50%, theoretical discussion of these results cannot lead to a reliable interpretation.

2. Asymmetric Hydrogenation of Imino-derivatives of α-Keto-acids

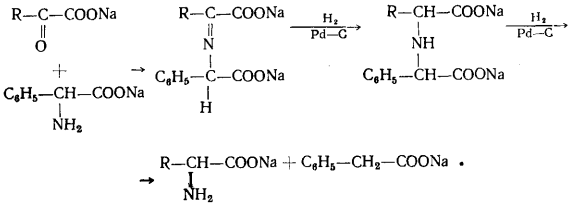
The asymmetric synthesis of α-amino-acids by the catalytic hydrogenation of the imino-derivatives of keto-acids has been most thoroughly investigated. The interest in this reaction is due in the first place to the fact that it constitutes a model of the biochemical transamination of amino-acids in the living organism, which consists in the reversible transfer of the amino-group from the amino-acid to an α-keto-acid without the intermediate formation of ammonia.

In 1939 Knoop and Martius [25] achieved the synthesis of octopine by the reaction of L-arginine with pyruvic acid with simultaneous hydrogenation of the C=N bond over platinum oxide in aqueous solution. The maximum yield of crude octopine reached 85%:



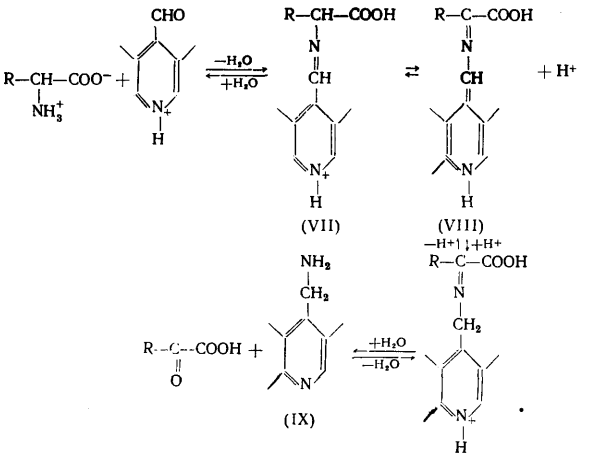
Later Herbst and Swart [26] showed that the product formed in this reaction is iso-octopine—a diastereoisomer of natural octopine containing an alanine residue with the L-configuration. Thus in this case L-arginine induces the formation of a new dissymmetric centre with predominantly the L-configuration.

Recently Harada [27,28] noted that sodium phenylglycinate readily splits into ammonia and phenylacetic acid on hydrogenation in aqueous solution in the presence of palladium or palladium hydroxide on charcoal. Using these data, he achieved a number of asymmetric syntheses, hydrogenating a mixture of sodium D- or L-phenylglycinate with α-keto-acids over the above catalysts in aqueous solution. The reaction probably takes place by the mechanism



In this way he obtained D- and L-alanine with an optical purity of 31–53% in a yield of 28–41%, D- and L-α-amino butyric acids with an optical purity of 24–39% in a yield of 38–41%, and D-glutamic acid with an optical purity of 45–58% in a yield of 25%. It is interesting to note that L-phenylglycine induces the formation of L-amino-acids and D-phenylglycine the formation of D-amino-acids. Harada essentially achieved the reductive asymmetric transamination reaction.

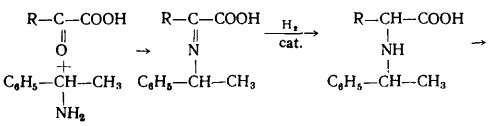
The mechanism of biochemical transamination has been to a considerable degree elucidated and consists in the reductive amination of α-keto-acids by the amino-acid, the process being catalysed by enzymes—amino-transferases. The non-protein component of amino-transferases is pyridoxal phosphate, which plays the role of the agent transferring amino-groups from amino-acids to α-keto-acids [29,30]:

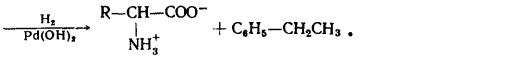


Pyridoxal phosphate forms with the α-amino-acid a Schiff base (VII), from the α-carbon atom of which a proton is readily removed. If the proton adds to the –CH= group of the intermediate (VIII) and then the >C=N– bond is hydrolysed, the final reaction products are an α-keto-acid and pyridoxamine phosphate (IX). The reverse reaction of compound (IX) with the α-keto-acid is a transamination process, the stereochemistry of which is of interest. Enzymes evidently create an asymmetric environment for the strictly stereospecific addition of H to compound (VIII) with formation of compound (VII) and finally of the amino-acid.

However, together with the enzymes, the optically active amino-acid involved in the transamination probably also has an asymmetrising effect. To elucidate this question, Longenecker and Snell [31] carried out the non-enzymic transamination between D- and L-alanine or D- and L-phenylalanine and α-oxoglutaric acid in the presence of a copper(II) complex of pyridoxal. It was found that, regardless of temperature (37–100°C), an excess of glutamic acid with the same configuration as that of the α-amino acid used was always formed, although it did not exceed 10%. Thus 55% of L-glutamic acid and 44.9% of D-glutamic acid was formed when L-phenylalanine was used, while in the presence of D-phenylalanine the yields were 52.7% of D-glutamic acid and 47.3% of L-glutamic acid. When racemic initial amino-acids were employed, racemic glutamic acid was produced. Similar results were obtained also when alanine was the starting material. The data of Longenecker and Snell [31] suggest that in biochemical transamination the main asymmetrising effect is due to enzymes.

Subsequent studies on non-enzymic hydrogenation of optically active imino-derivatives of α-keto-acids demonstrated the possibility of a fairly considerable asymmetrising effect of the optically active component on the stereochemistry of the addition of hydrogen. Hiskey and Northrop [32] used D-(+)- and L-(–)-α-methylbenzylamine as the asymmetrising agent and carried out the hydrogenation according to the following scheme:





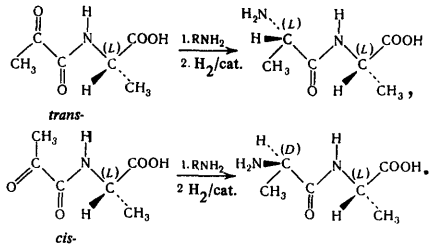
The hydrogenation was performed in the presence of palladium or its hydroxide on charcoal. Optically active alanine, phenylalanine, α-aminobutyric acid, and valine with a high degree of optical purity (56–91%) were obtained in this way. The configuration of the α-amino-acid formed was that of the α-methylbenzylamine employed. The optical purity of the α-amino-acid depended on both the type of catalyst and on the size of the group R in the α-keto acid. In the hydrogenation of the derivative of D-(+)-α-methylbenzylamine and pyruvic acid over the Pd/C catalyst the excess of the D-isomer in the alanine isolated was 85.2% (yield 47.9%), over $Pd(OH)_2/C$ the excess was 91.1% (yield 78%), and over PtO_2 the excess was 56.3% (yield 59.2%). With increase in the bulk of the group R of the α-keto-acid, the hydrogenation becomes less stereospecific: the optical yield of α-amino-acids decreases from 82% for alanine (R = CH_3) to 63% for α-aminobutyric acid (R = CH_2CH_3) and 28% for valine [R = $CH(CH_3)_2$].

In 1965 Hiskey and Northrop published the results of an interesting investigation [33] in which the asymmetrising role of the amine residue in the azomethine group was assessed. This assessment was achieved by investigating the competing effect of dissymmetric groups at the imino- and carboxy-groups attached to the pyruvic acid residue. For this purpose, the imino-derivatives of *N*-pyruvyl-L-alanine or *N*-pyruvylglycine were hydrogenated together with optically active α-methylbenzylamines. As was to be expected, according to Hiskey and Northrop [32], with *N*-pyruvylglycine, L-(−)- and D-(+)-α-methylbenzylamines lead to the formation of L-alanylglycine (optical yield 53.5%) and D-alanylglycine (optical yield 58%) respectively. The lower optical yield of alanylglycine compared with alanine (82%)[32] or phenylalanine (74%) is attributed by the authors either to an increase in the bulk of the substrate, which leads to a decrease of the stereospecificity of the hydrogenation or to an unfavourable interaction of the catalyst and the substrate due to the presence in the latter of an additional polar group. The second explanation seems more probable, since L-glutamic acid with a relatively low optical yield (35%) was isolated in the hydrogenation of α-oxoglutaric acid (R = CH_2CH_2COOH) in the presence of three equivalents of L-(−)-α-methylbenzylamine. Reductive amination of *N*-pyruvyl-L-alanine in the presence of D-(+)-α-methylbenzylamine led to an excess of D-alanyl-L-alanine (diastereoisomer ratio DL : LL = 74 : 26) and in the presence of L-(−)-α-methylbenzylamine to an excess of L-alanyl-L-alanine (LL : DL = 64 : 36).

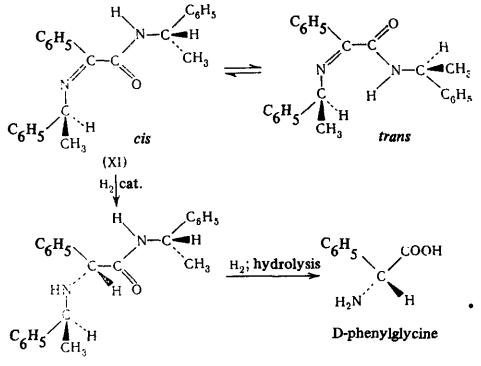
This result indicates a more significant asymmetrising effect of the optically active α-methylbenzylimino-group compared with the amino-acid residue at the carboxy-group. To estimate the asymmetrising effect of the L-alanine residue, reductive amination of *N*-pyruvyl-L-alanine was carried out in the presence of benzylamine. An excess of D-alanyl-L-alanine was then obtained (DL : LL = 67 : 33). The authors regard this result as unexpected since, according to Prelog's rule, the L-alanine residue should induce the formation of a new alanine residue with the D-configuration (on the assumption that the carboxy-group is larger than the methyl group).

Kanai and Mitsui [34] suggest, however, that in the reductive amination of *N*-pyruvyl-L-alanine the significant factor is the predominant conformation of the substrate.

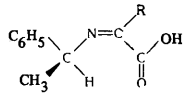
Probably the cisoid conformation predominates, which in fact leads to the formation of D-alanyl-L-alanine:



Kanai and Mitsui arrived at this hypothesis on the basis of the results of the asymmetric hydrogenation of an L-(−)-α-methylbenzylammonium salt (X) and L-(−)-α-methylbenzylamide of L-(−)-α-methylbenzyliminophenylglyoxylic acid (XI) in the presence of the following catalysts: Raney nickel, PtO_2, 5% Pd/C, and 10% $Pd(OH)_2/C$. In the hydrogenation of the salt (X) over $Pd(OH)_2/C$ L-phenylglycine was obtained with an optical yield of 73%, which is similar to the results of Hiskey and Northrop [32]. However, in the hydrogenation of the amide (XI) D-phenylglycine is formed regardless of the type of catalyst. On this basis, Kanai and Mitsui concluded that the predominant conformation of the substrate (XI) is cisoid. It is noteworthy that the optical purity of the D-phenylglycine is low (1–7%).



Harada and Matsumoto [35], who investigated the stereochemistry of the reductive amination of α-keto-acids, believed that the mechanism of Kanai and Mitsui [34] cannot explain the effect of the bulk of the substituents in α-keto-acids on the optical purity of the α-amino-acids formed. Indeed if the substrate molecule were in the cisoid conformation, the substituents R of the α-keto-acids should have scarcely any effect on the mode of addition of hydrogen atoms.

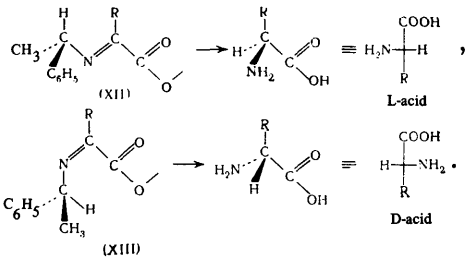


Like Hiskey and Northrop [32], Harada and Matsumoto [35] showed that the optical purity of the α-amino-acid formed decreases with increase in the size of the substituent R:

$$CH_3 > C_2H_5 > C_6H_5 > C_6H_5CH_2 .$$

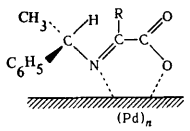
They believe that the most probable conformation of the substrate molecule is the transoid conformation (XII) or

(XIII), the structure (XII) being more probable because of smaller steric hindrance:



The mechanism shows that, when L-α-methylbenzylamine is used, the conformation (XII) leads to the formation of the L-amino-acid, while with the conformation (XIII) the D-amino-acid is formed. As the size of the group R increases, its interaction with the hydrogen atom at the asymmetric carbon atom becomes more pronounced, which may lead to an increase in the fraction of the structure (XIII) and this in turn results in a decrease of the optical purity of the product.

No less important is the examination of the above structures from the standpoint of their capacity to interact with the catalyst. Chang and Hartung [36] believed that such interaction may result in the formation of a rigid cyclic substrate species on the surface of the catalyst. From this point of view, the structure (XII) is to be preferred, since, in contrast to the structure (XIII), it can readily form a five-membered cyclic structure with the catalyst:

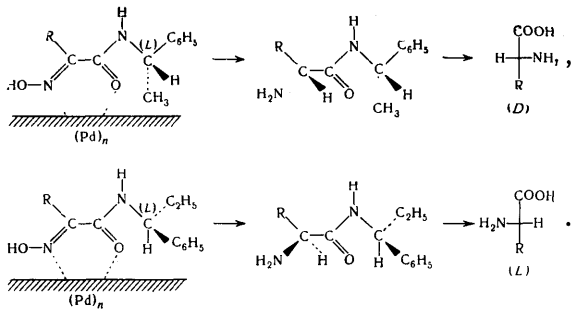


It is readily seen that complex-formation does not lead to a change in the configuration of the α-amino-acid formed.

The replacement of a methyl group by an ethyl group in the optically active alkylbenzylamine [35] leads to a decrease of the optical purity of the hydrogenation products. Prelog established [18,19] that this is caused by a decrease of the difference in the bulk of the substituents at the asymmetric carbon atom of the asymmetrising agent and hence a decrease of the relative steric hindrance to the approach of hydrogen from the two sides of the group >C=N–. This leads to a decrease of the stereospecificity of the hydrogenation and of the optical purity of the α-amino-acids produced.

On the basis of experimental data for the hydrogenation of the oximes of D- and L-α-methylbenzylamide and D- and L-α-ethylbenzylamide of phenylglyoxylic acid and also the Schiff bases formed by benzylamine with the isobutyl esters of *N*-pyruvyl-L-alanine, *N*-pyruvyl-L-valine, and *N*-pyruvyl-D-valine, Harada and Matsumoto [35] gave the most likely explanation of the anomalous synthesis of D-alanyl-L-alanine achieved by Hiskey and Northrop [33].

The hydrogenation of the oximes of L- and D-α-methylbenzylamide of phenylglyoxylic acid led, contrary to Prelog's rule, to the formation of D- and L-phenylglycine respectively. On the other hand, when L- and D-α-ethylbenzylamine were used as the asymmetrising agent, L- and D-phenylglycine were obtained respectively, in agreement with Prelog's rule. Harada and Matsumoto [35] suggest that the substrate molecule is in the cisoid conformation, capable of forming a complex with palladium:

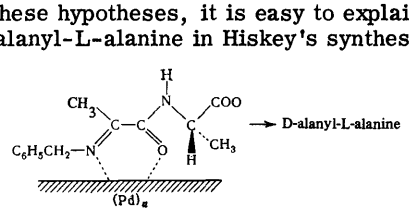


They attribute particular importance to the effect of the catalysts on the conformation of the optically active part of the substrate molecule. The L-α-ethylbenzyl group cannot have the same conformation as the L-α-methylbenzyl group because of the greater bulk of the ethyl group compared with the methyl. Therefore the L-α-ethylbenzyl group rotates with the hydrogen atom, which is least bulky, directed towards the catalyst surface and then the *cis*-addition of hydrogen, occurring on the least hindered side opposite to the plane of the image, leads to the formation of the L-amino-acid.

The hydrogenation of the Schiff bases formed by benzylamine with isobutyl esters of pyruvyl-L-alanine, pyruvyl-L-valine, and pyruvyl-D-valine, which is a closer model of Hiskey's synthesis of D-alanyl-L-alanine, also confirmed these conclusions. When these substrates form complexes with palladium, the methyl group of the alanine derivative and the isopropyl group of the valine derivative lead to different conformations of the asymmetrising agent (in consequence of the different steric hindrance to the interaction with the catalyst surface), exactly as in the preceding case. The Schiff base of the isobutyl ester of pyruvyl-L-alanine gave D-alanyl-L-alanine, while the Schiff bases of the isobutyl esters of pyruvyl-L-valine and pyruvyl-D-valine led to the formation of L-alanyl-L-valine and D-alanyl-D-valine respectively (yield 11–15%, optical purity 32–64%).

The different conformations induced by the groups of the optically active part of the substrate having different sizes (methyl or ethyl, methyl or isopropyl) may be due to the steric hindrance to the interaction between substrate molecules and the catalyst.

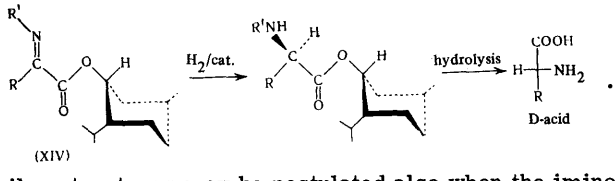
Using these hypotheses, it is easy to explain the formation of D-alanyl-L-alanine in Hiskey's synthesis:



The asymmetric catalytic hydrogenation of (–)-menthyl esters of the imino-derivatives of α-keto-acids was achieved by Matsumoto and Harada [37]. The hydrogenation was carried out over palladium and $Pd(OH)_2$ on charcoal and the amino-acids were isolated by hydrolysing the hydrogenation products in an alkaline medium. D-amino-acids were always obtained from the (–)-menthyl esters of the hydroxyimino- and benzimino-derivatives of pyruvic, α-oxobutyric, and phenylglyoxylic acids, regardless of the type of catalyst employed. The products were D-alanine with an optical purity of 11.0–13.6% and a yield of 67–79%,

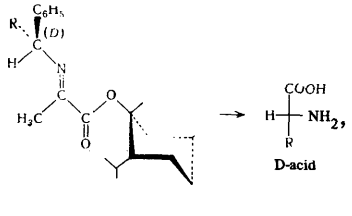
D-aminobutyric acid with an optical purity of 9.44–10.3% and a yield of 62–74%, and D-phenylglycine with an optical purity of 22.7–24.9% (44.2–49.1%)† and a yield of 84–88%. The hydrogenation of the hydroxyimino-derivative led to the formation of the α-amino-acid with a higher optical purity than was obtained with benzimino-derivatives. The type of catalyst employed had virtually no effect on the yield and optical purity of the α-amino-acid, but the benzimino-derivatives of (–)-menthyl esters of pyruvic and α-oxobutyric acids could not be hydrogenated over the Pd/C catalyst. Phenylglycine was synthesised only from the hydroxyimino-derivative of phenylglyoxylic acid, since the benzimino-derivative could not be prepared.

The most interesting results were obtained in the hydrogenation of L-(–)- and D-(+)-α-methylbenzylimino-derivatives of (–)-menthyl pyruvate. The L-(–)-α-methylbenzylimino-derivative gave L-alanine with an optical purity of 16–18% (19–24%) and a yield of 57–62% and the D-(+)-α-methylbenzylimino-derivative gave D-alanine with an optical purity of 56–64% (59–66%) and a yield of 61–67%. If it is remembered that, according to this investigation the (–)-menthyl residue induces the formation of the D-amino acid and according to Hiskey and Northrop [32] the D-(+)-α-methylbenzylimino-residue also induces the formation of the D-acid, then the high optical purity of the D-alanine obtained in the hydrogenation of the D-(+)-α-methylbenzylimino-derivative of (–)-menthyl pyruvate is evidence that the two asymmetrising agents act in accord. On the other hand, the formation of L-alanine in the hydrogenation of the L-(–)-α-methylbenzylimino-derivative of (–)-menthyl pyruvate is evidence of the greater asymmetrising effect of the α-methylbenzylimino-group compared with the (–)-menthyl ester residue, which is consistent with the result of the investigation [33]. The authors explain [37] the steric specificity of the reaction on the basis of the concepts of Cram and Prelog. It is suggested that the most probable structure of the imino-derivative of the (–)-menthyl esters of the α-keto-acid is (XIV). The molecules are adsorbed on the surface of the catalyst from the less hindered side, as a result of which hydrogen atoms will attack the C–N bond from the side opposite to that of the plane of the representation of the mechanism. The products are α-amino-acids with the D-configuration:

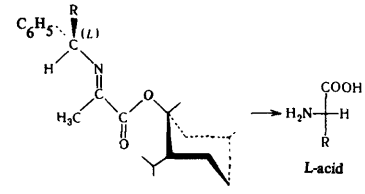


(XIV)

Similar structures may be postulated also when the imino-derivatives of optically active alkylbenzylamines and (–)-menthyl esters of α-keto-acids are employed [35]:



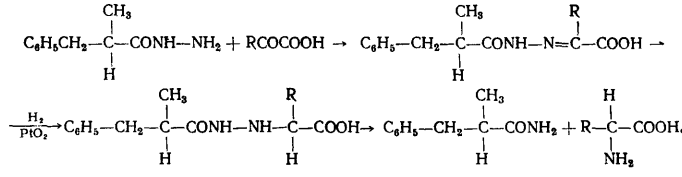
†The figures in brackets indicate, here and subsequently, the optical purity of the amino-acids isolated as the 2,4-dinitrophenyl derivatives.



This mechanism also explains why α-ethylbenzylamine leads to a lower optical purity of the final product than does α-methylbenzylamine.

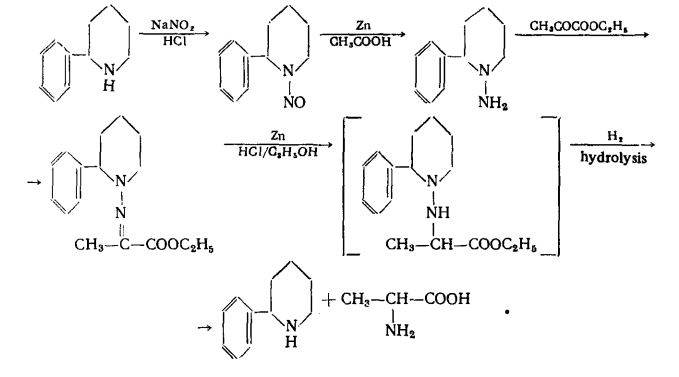
Apart from the asymmetrising agents examined above, such as optically active amino-acids, α-alkylbenzylamines, and (–)-menthol, other optically active substances have also been employed.

Akabori and Sakurai [38] used the optically active hydrazide of D-methylbenzylacetic acid as the asymmetrising agent. The imino-derivatives obtained from the hydrazide and α-keto-acids were hydrogenated over PtO_2 and the optically active α-amino-acids were isolated after the elimination of the asymmetrising agent:



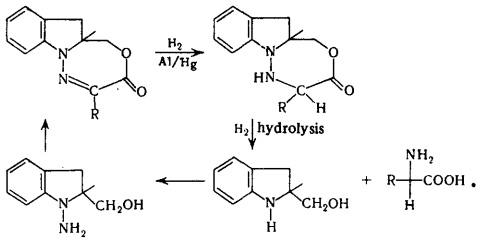
However, the optical yield of the α-amino-acids was low. L-Alanine (R = CH_3) with $[\alpha]_D^{19} = +1.21°$ (8% of asymmetric synthesis) and L-phenylalanine (R = $C_6H_5CH_2$) with $[\alpha]_D^{16} = -1.55°$ (4% of asymmetric synthesis) were obtained in this way.

Kost and coworkers [39,40] used anabasine (the alkaloid of *Anabasis Aphylla*) as the asymmetrising agent. Anabasine was converted into the *N*-amino-compound by nitrosation with subsequent reduction of the nitroso-group. The interaction of *N*-aminoanabasine with ethylpyruvate gave an optically active hydrazone, which was reduced with zinc in alcoholic hydrochloric acid:



This led to the formation in the molecule of a second dissymetric centre. Simultaneously (or subsequently) in the second stage the N–N bond is hydrogenolysed and optically active D-alanine is formed with an optical purity of 40% in a yield of 10%. Despite the low yield of D-alanine (which precludes the conclusion that asymmetric synthesis really takes place), it is noteworthy that the reaction regenerates the asymmetrising agent (anabasine) with virtually the initial (90%) optical activity.

A high optical yield in the synthesis of α-amino-acids was achieved by McCaully [41]. He carried out the asymmetric hydrogenation of an optically active hydrazonolactone with aluminium amalgam with preferential formation of one diastereoisomeric hydrazinolactone. Hydrogenolysis of the hydrazinolactone in an acid medium gives the optically active α-amino-acid and optically active 2-hydroxymethylindoline, which is converted into 1-amino-2-hydroxymethylindoline by nitrosation and subsequent reduction.



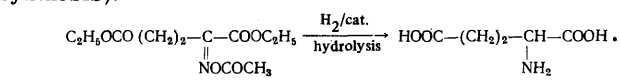
When the last compound is condensed with an α-keto-ester, the hydrazonolactone is formed anew. Optically active alanine (R = CH_3) with an optical yield of 82% and α-aminobutyric acid (R = C_2H_5) with an optical yield of 98% were obtained in this way, the reaction being virtually stereospecific in the second case.

3. Hydrogenation in the Presence of Dissymmetric Catalysts

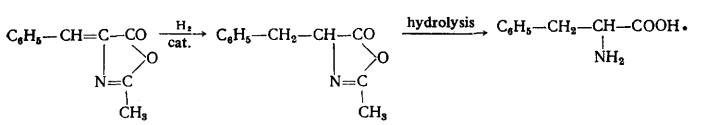
The hydrogenation of unsaturated precursors of α-amino-acids with an optically active asymmetrising group in the initial molecule was described above. This section deals with the formation of optically active α-amino-acids in the hydrogenation of unsaturated optically inactive precursors under the influence of dissymmetric catalysts. Such catalysts are of particular interest, since asymmetric syntheses, analogous to those occurring in the nature under the influence of enzymes, takes place in their presence.

In 1956 Akabori and coworkers [42-44] described the preparation of a dissymmetric heterogeneous catalyst based on the fact that many enzymes (oxidoreductases) are metalproteins. The catalyst, which consisted of a dissymmetric carrier (silk fibroin or acetylfibroin [45]) on which palladium was absorbed, was obtained by reducing the fibroin–$PdCl_2$ complex. The properties of the catalyst were described in detail by Izumi [46-48].

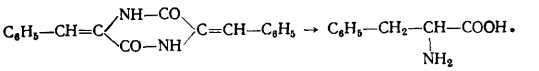
When diethyl α-acetoxyiminoglutarate was reduced over this catalyst at 50°C and 80 atm, optically active L-glutamic acid was formed ($[\alpha]_D^{15} = +2.25°$, 39% of asymmetric synthesis):



Ethyl α-acetoxyiminophenylpropionate was reduced to D-phenylalanine (yield 25%, optical purity 26.3%) in a similar manner at 70°C and 90 atm. The highest optical purity of D-phenylalanine (35%) was achieved in the hydrogenation under the same conditions of 4-benzylidene-2-methyloxazol-5-one, although the yield of D-phenylalanine was only 6.5%:



D-phenylalanine with the specific rotation $[\alpha]_D^{15} = +8.0°$ was obtained in the hydrogenation of dibenzylidenedioxopiperazine:



The maximum yield (80%) of phenylalanine was achieved in the hydrogenation of α-acetamidocinnamic acid, although the product was inactive.

The study of the infrared spectra of the dissymmetric catalyst [48] showed that, when $PdCl_2$ is adsorbed on silk fibroin, chelate bonds are formed between $PdCl_2$ and fibroin groups such as NH, OH, COOH, and CONH. When the chelate is reduced with hydrogen, the chelate bonds break down and the fibroin resumes its initial structure. The study of X-ray diffraction by the catalyst suggests that part of the palladium in the latter is in the cryptocrystalline state and the remainder assumes the dissymmetric structure of the fibre and this is in fact responsible for the asymmetric synthesis. However, the latest studies suggest that the mechanism of the asymmetrising effect of the dissymmetric catalyst probably consists in the initial asymmetric adsorption of the reactant on the surface of the dissymmetric carrier with subsequent non-stereospecific catalysis [3].

One of the methods developed recently for imparting stereospecificity to optically inactive hydrogenation catalysts consists in their modification with optically active substances—for example α-hydroxy-acids or α-amino-acids. Thus Isoda et al. [49] described a new dissymmetric hydrogenation catalyst based on an amino-acid—palladium and an amino-acid—Raney nickel complex. Best results were achieved when optically active tyrosine was employed. L-Glutamic acid was obtained in this way in the reduction of diethyl α-acetoxyiminoglutarate and D-phenylalanine was synthesised by the reduction of 4-benzylidene-2-methyloxazol-5-one. However, the efficiency of this catalyst was lower than that of palladium on silk fibroin prepared by Akabori and the experimental results were poorly reproducible.

L-Phenylalanine was synthesised similarly by the hydrogenation of α-acetamidocinnamic acid over palladium deposited on charcoal and modified with L-methionine [50].

Studies on catalysts of this type are being vigorously continued at the present time. Best results are obtained with Raney nickel treated with aqueous solutions of optically active substances [51,52]. In the most successful experiments a mixture of methyl α-hydroxybutyrates, consisting of 75% of the L-form and 25% of the D-form was obtained by the hydrogenation of methyl acetoacetate, used as a model compound, over Raney nickel modified with D-tartaric acid.

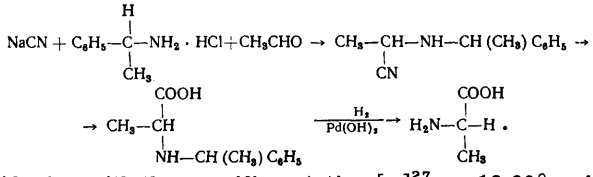
Asymmetric catalytic hydrogenation was achieved in many cases in the presence of optically active substances. Thus Isoda et al. [53] obtained optically active glutamic acid in the hydrogenation of α-hydroxyiminoglutaric acid in the presence of (+)-camphor and (+)-borneol over Raney nickel. Nakazaki [54] achieved the asymmetric hydrogenation of α-acylaminocinnamic acid over Raney nickel in the presence of glucose. After the hydrolysis of the hydrogenation products, optically active D-phenylalanine was isolated with the rotation $[\alpha]_D^{15}$ ranging from +2.22° to 3.58°, depending on the reaction conditions.

In the experiments described above the active substances constitute an optically active medium rather than disymmetric organic catalysts, since they show no independent catalytic effect.

III. ASYMMETRIC SYNTHESIS OF α-AMINO-ACIDS BY CONDENSATION METHODS

1. The Strecker Synthesis

In 1963 Harada [55] achieved the asymmetric synthesis of alanine by the Strecker reaction. The asymmetrising agent was (−)-α-methylbenzylamine. The synthesis consisted in the interaction of acetaldehyde with HCN or NaCN and (−)-α-methylbenzylamine in methanol at 20°C, the hydrolysis of the resulting aminonitrile to *N*-(α-methylbenzyl)amino-acid, and the elimination of the methylbenzyl group by catalytic hydrogenolysis over $Pd(OH)_2$ by Hiskey's procedure [32]:

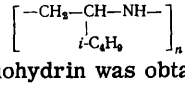


L-Alanine with the specific rotation $[\alpha]_D^{27} = +13.99°$, which corresponds to 95% of asymmetric synthesis, was obtained in this way. Subsequently Harada and Fox [56] carried out this synthesis starting with the previously prepared acetaldehyde cyanohydrin. Depending on the duration of the reaction, L-alanine was obtained with optical purities in the range 86–99% (after one recrystallisation).

The reaction mechanism is still obscure. However, the authors [56] suggest that the most likely cause of the asymmetric synthesis is different rates of the reactions of the D- and L-cyanohydrins with the (−)-amine.

It is believed [57] that this synthesis constitutes a good model of the formation of active α-amino-acids in the prebiological period of the development of the earth.

Interesting results were obtained by Tsuboyama [58] in the cyanohydrin synthesis from benzaldehyde and hydrocyanic acid in benzene in the presence of optically active poly-L-isobutylethyleneimine as the catalyst:

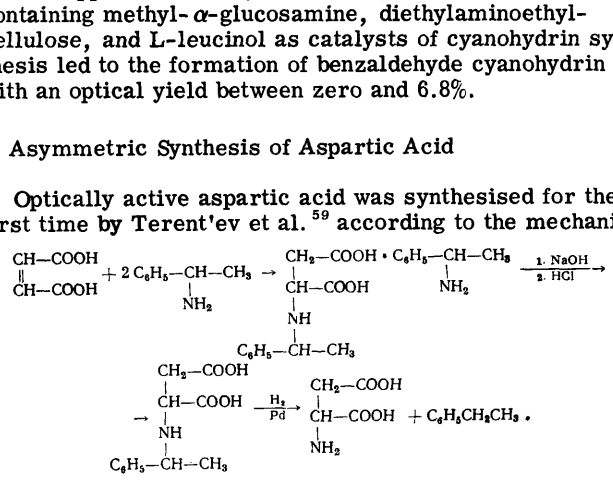


Benzaldehyde cyanohydrin was obtained with an optical yield up to 20%. The asymmetrising effect of the catalyst was attributed by the author to the stereoregularity of the polymer, the presence of dissymmetric centres in the main chain, and the spiral structure of the polymer, which enhances the asymmetrising effect.

The application of styrene–divinylbenzene copolymers containing methyl-α-glucosamine, diethylaminoethylcellulose, and L-leucinol as catalysts of cyanohydrin synthesis led to the formation of benzaldehyde cyanohydrin with an optical yield between zero and 6.8%.

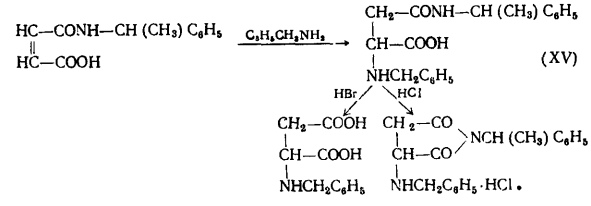
2. Asymmetric Synthesis of Aspartic Acid

Optically active aspartic acid was synthesised for the first time by Terent'ev et al. [59] according to the mechanism



The reaction of maleic acid with (−)-α-methylbenzylamine yields a salt the decomposition of which gives an *N*-substituted aspartic acid. The acid consists of two types of crystals with different solubilities—large, well formed crystals in an amount greater than small crystals combined into spherical pellets. When the large crystals were debenzylated over palladium black, D-aspartic acid with an 88% optical purity was obtained. The small crystals yielded racemic aspartic acid. When (+)-α-methylbenzylamine was employed, two types of crystals were also obtained, in approximately equal amounts. After debenzylation the large crystals gave L-aspartic acid ($[\alpha]_D^{20} = +4.83°$) and the small crystals the racemic acid. The authors [59] suggest that in this case there is either partial asymmetric synthesis or the diastereoisomers are recrystallised.

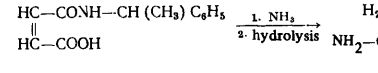
Livshits and Singerman [60], who repeated Terent'ev's experiment, reject the occurrence of asymmetric synthesis in this process and believe that true asymmetric synthesis of aspartic acid takes place when benzylamine adds to the double bond of poly-(+)-α-methylbenzylamide of maleic acid:



(XV)

Thin-layer chromatography of the amide (XV) showed the presence of only one substance. Its hydrolysis in a sealed tube at 100°C with 20% hydrochloric acid led to the formation of the imide. On the other hand, when the imide (XV) was refluxed with 48% hydrobromic acid, the product was *N*-benzyl-L-aspartic acid of 60% optical purity, which the authors [61] believe may be debenzylated with complete retention of the configuration.

Subsequently Vlasova [62], who carried out the reaction of mono-(−)-α-methylbenzylamide of maleic acid with ammonia, really achieved the asymmetric synthesis of D-aspartic acid with an optical purity of 80% and a yield of 90%:



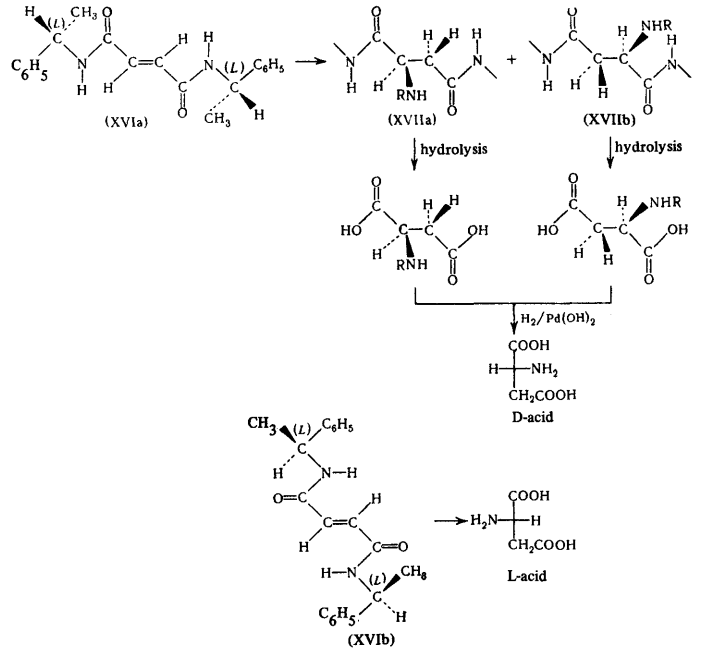
A detailed study of the asymmetric synthesis of aspartic acid from maleic and fumaric derivatives was carried out by Harada and Matsumoto [63]. The following reactions were investigated: (1) the reaction of L-(−)- and D-(+)-α-methylbenzylamine with *NN'*-di-L- and *NN'*-di-D-α-methylbenzylfumaramide (L- and D-fumaramide); (2) the reaction of L-(−)- and D-(+)-α-methylbenzylamine with diethyl maleate and diethyl fumarate. Debenzylation was carried out in the presence of $Pd(OH)_2$ by Hiskey's procedure [32].

The reaction of L-fumaramide with L-(−)-α-methylbenzylamine gave D-aspartic acid with an optical purity of 10.2% (15.3% in the form of the dinitrophenyl derivative) and a yield of 64%. D-Fumaramide and L-(−)-α-methylbenzylamine reacted to form L-aspartic acid with an optical purity of 11.0% (13.7%). The reaction of diethyl maleate with D-(+)-α-methylbenzylamine yielded D-aspartic acid with an optical purity of 12.2% (15.4%) and the reaction with L-(−)-α-methylbenzylamine gave L-aspartic acid. Similarly the interaction of diethyl fumarate with L-(−)-α-methylbenzylamine led to the formation of L-aspartic acid with an optical purity of 7.5% (4.6%) and the interaction with

D-(+)-α-methylbenzylamine gave D-aspartic acid with an optical purity of 6.3% (4.5%).

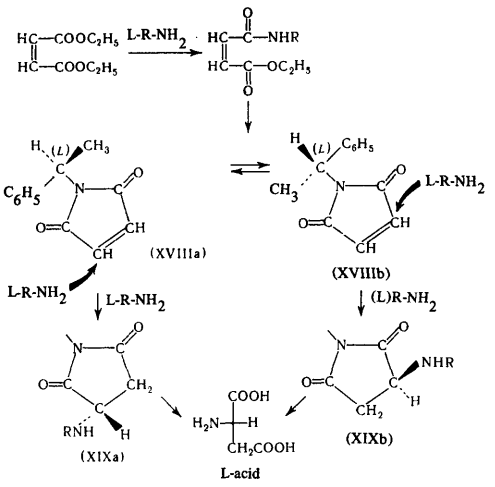
The principal asymmetrising effect in the reaction of L- and D-fumaramide with optically active amines is shown by optically active amide groups. Amides with the L-configuration induce the formation of D-aspartic acid and conversely. The configuration of the amine entering into the reaction apparently does not have a decisive influence on the configuration of the acid formed. Indeed, when optically active amines are replaced by benzylamine, the situation does not change: D- and L-fumaramide yield L- and D-aspartic acid respectively. However, the optical purity of the acids obtained is then lower.

Harada and Matsumoto explained the configuration of the final product on the basis of the hypotheses of Cram and Prelog:

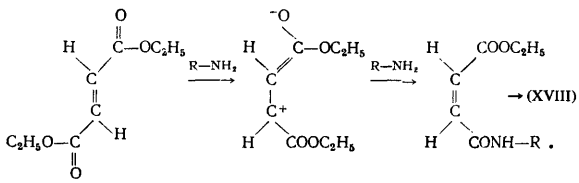


The possible conformations of L-fumaramide are cisoid (XVIa) and transoid (XVIb). The addition of L- or D-α-methylbenzylamine to the double bond of fumaramide in the cisoid conformation takes place preferentially from the least hindered front side of the plane of the image, since both methyl groups are on the reverse side. In this case both addition products, (XVIIa) and (XVIIb), are identical and yield aspartic acid with the D-configuration. The addition of the amine to fumaramide in the transoid conformation (XVIb) leads ultimately to the formation of L-aspartic acid. However the transoid conformation of L-fumaramide (XVIb) is energetically less favourable, since, by virtue of steric hindrance, it cannot be planar. It was shown with the aid of Dreiding stereomodels that in the transoid conformation the distance between the hydrogen of the amide group and the hydrogen at the β-carbon atom is 1.65 Å. Since the van der Waals radius of the hydrogen atom is 1.15 Å, these two hydrogen atoms overlap and prevent the formation of a planar molecule. On the other hand, in the cisoid conformation there is no such steric hindrance and therefore the molecule can form a planar structure.

In the reaction of diethyl maleate and diethyl fumarate with L- or D-α-methylbenzylamine the first stage is the formation of the amides of these acids, which then cyclise to the imide (XVIIIa) or (XVIIIb) as shown below:

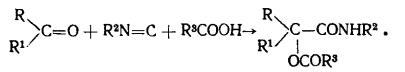


Regardless of the conformation of the *N*-alkylmaleimide (XVIIIa) or (XVIIIb), it is attacked by L-α-methylbenzylamine from the least hindered side (indicated by arrows) forming a derivative of L-aspartic acid. The intermediate addition product—succinimide (XIX)—was isolated as the main reaction product, which confirms this mechanism. Since (XIX) is formed also from diethyl fumarate, Harada and Matsumoto[63] suggested the possibility of the conversion of fumarate into maleate in the reaction



3. Asymmetric Synthesis of α-Amino Acids by the Ugi Reaction‡

As early as 1921 Passerini[67] observed that isonitriles readily condense with carbonyl compounds in the presence of carboxylic acids, forming the amides of α-acyloxy-acids:

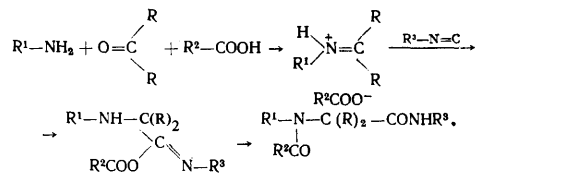


The reaction takes place under very mild conditions (between −20° and +20° C) with almost quantitative yields of the final products[68]. It is noteworthy that the use in the Passerini reaction of an optically active acid leads to the preferential formation of one of the two possible diastereoisomers[69].

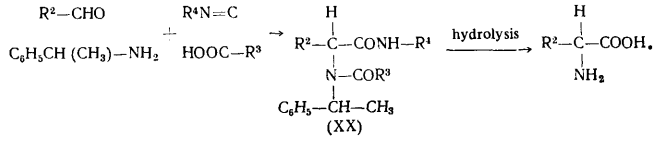
In 1960 Ugi[70] carried out this condensation in the presence of a fourth component (an amine), which led to the discovery of the reaction involving the aminoalkylation of isonitriles by immonium salts, formed from the carbonyl

‡For further details of the reaction, see the reviews of Ugi[64,65] and Gambaryan[66].

compound, the amine, and the acid. The reaction gives under mild conditions almost quantitative yield of the α-amino-acid derivative:



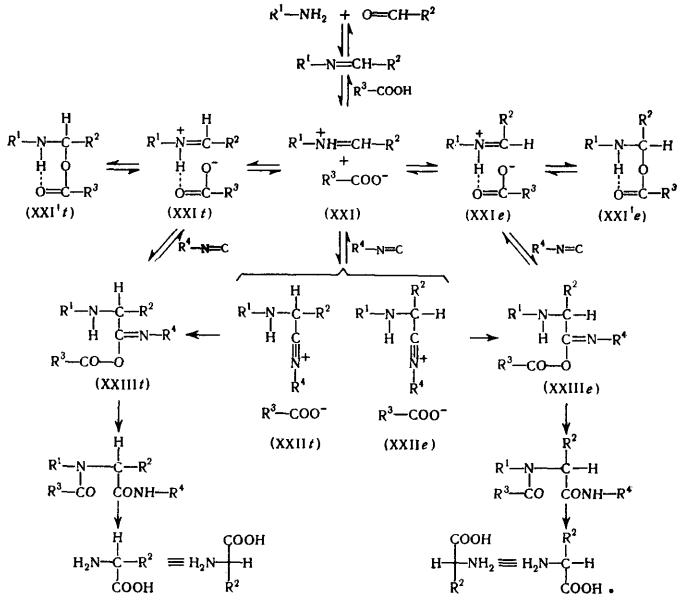
When an optically active amine, for example α-methylbenzylamine, is used, one of the diastereoisomers is formed preferentially and its hydrolysis gives the optically active α-amino-acid [71-73]:



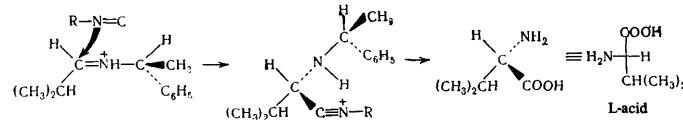
The configuration of the asymmetric carbon atom produced in compound (XX) depends both on the configuration of the asymmetrising agent (the amine) and on the reaction conditions (polarity of the solvent, concentrations of the reactants, and temperature). Thus the interaction of isobutyraldehyde [$R^2 = CH(CH_3)_2$], D-(+)-α-methylbenzylamine, benzoic acid ($R^3 = C_6H_5$), and t-butyl isocyanide [$R^4 = C(CH_3)_3$] at $-70°C$ and about 1 molar reactant concentrations in methanol (conditions *A*) led to the preferential formation of L-valine, while at 0° C and reactant concentrations about 0.1 molar (conditions *B*) D-valine was formed. Similar relations were observed also when other aldehydes, including optically active ones, were employed in the reaction. For example, under conditions *A* the reaction of L-(−)-α-methylbenzylamine, benzoic acid, t-butyl isocyanide, and butyraldehyde ($R^2 = n\text{-}C_3H_7$) or L-(+)-ethylmethylacetaldehyde [$R^2 = L\text{-}CH(CH_3)C_2H_5$] gives D-norvaline or D-alloisoleucine, while under conditions *B* the products are L-norvaline or L-isoleucine respectively. Similarly, when D-(+)-α-methylbenzylamine is employed, the products under conditions *A* are L-norvaline or L-isoleucine and under conditions *B* D-norvaline and D-alloisoleucine respectively. Compounds of type (XX) are usually formed with an optical purity in the range 70–75% and yields of 70–95%; their hydrolysis in hydrochloric acid results in a quantitative yield of the α-amino-acids with the retention of the configuration and optical purity [73].

Thus, when the temperature is reduced and the concentration of the reactant is increased, the configuration opposite to that of the initial amine is induced at the newly formed asymmetric carbon atom, and, conversely, on raising the temperature and lowering the reactant concentration, a compound with the same configuration is formed. The reversal of the configurational relation between the induced and inducing dissymmetric centres as a function of reaction conditions is explained by the fact that the Ugi reaction takes place under different conditions by two stereochemically different mechanisms [72,74-77].

All the reactions of isonitriles, including the Ugi reaction, reduce essentially to electrophilic α-addition of the cationic and anionic centres to the isonitrile carbon atoms. Initially the azomethine derivative is formed from the carbonyl compound and the amine. In a strongly polar medium it is present as a solvated non-oriented ion pair (XXI) with the carboxylic acid. In less polar solvents the azomethine derivatives and the carboxylic acids form hydrogen-bonded diastereoisomeric ion pairs (XXI*t*) and (XXI*e*), which may be in equilibrium with the adducts (XXI′*t*) and (XXI′*e*), where *t* denotes the *threo*-form, i.e. the diastereoisomer in which on direct combination both dissymmetric centres would have the identical configuration, and *e* denotes the *erythro*-form with different configurations of the dissymmetric centres. It is readily seen that the mechanism and stereochemistry of the α-addition of the immonium cation and the carboxylate anion to the isonitrile depend to a high degree on the polarity of the medium. This is either a two-stage process (conditions *B*): (XXI) → (XXII*t*, *e*) → (XXIII*t*, *e*), or a one-stage process (conditions *A*): (XXI*t*, *e*) → (XXIII*t*, *e*):



In strongly polar solvents, for example in ethylene glycol or methanol, at low reactant concentrations and high temperatures the ratio of the products [(XXIII*t*): (XXIII*e*)] of the addition of the solvated ion pair (XXI) to the isonitrile is determined by steric factors. The *threo*-isomer then forms preferentially, as can be seen in the case of the azomethine derivative obtained from L-(−)-α-methylbenzylamine and isobutyraldehyde:



The two-stage reaction *B* is a kinetically controlled process and the ratio of the reaction products (XXII*t*): : (XXII*e*) is determined by the steric strain of the conformation of the transition state, i.e. depends on the difference between the free energies of the transition states, which, as found for the reaction of L-(−)-α-methylbenzylamine, isobutyraldehyde, benzoic acid, and t-butyl isocyanide, is $\Delta F^{\neq}_{(XXI) \rightarrow (XXII e)} - F^{\neq}_{(XXI) \rightarrow (XXII t)} = 0.71$ kcal mole^{-1}. [74]

In a less polar medium, for example in ethanol and in methanol, at high reactant concentrations or at a low temperature the diastereoisomeric hydrogen-bonded ion pairs

(XXI*t*) and (XXI*e*) formed are in equilibrium, the position of which plays a decisive role in determining the steric course of the process (thermodynamically controlled reaction). Because of the smaller conformational strain, the *erythro*-isomer (XXI*e*) is energetically more favourable and therefore under the given conditions there is preferential formation of α-amino-acids having the configuration opposite to that of the initial amine. If the equilibrium (XXI*t*) ⇌ (XXI*e*) is established rapidly, the ratio of the products of the single-stage reaction A [(XXIII*t*) : (XXIII*e*)] may be determined by the Curtin–Hammett principle. Indeed, for the same reaction of L-(−)-α-methylbenzylamine, isobutyraldehyde, benzoic acid, and t-butyl isocyanide under conditions *A*, we have $\Delta F = F^{\neq}_{(XXI t) \rightarrow (XXIII t)} - F^{\neq}_{(XXI e) \rightarrow (XXIII e)} = 1.02$ kcal mole^{-1}. Evidently the experimental values of $\Delta F^{\neq}$ both for reaction *A* and *B* essentially confirmed the above hypotheses concerning the stereochemistry of these reactions. This concerns of course only the preferential occurrence of the reaction by mechanisms *A* and *B*. However, the high sensitivity of the Ugi reaction to changes in conditions, within the limits of which there is a possibility of controlled synthesis of both L- and D-amino-acid with a high optical purity and yield, makes it one of the most promising synthetic procedures for optically active α-amino-acids.

4. Application of Complexes in the Asymmetric Synthesis of α-Amino-acids

The stereospecificity of coordination compounds in certain reactions is well known[78]. However, only a few papers have been published[79,81,83] on studies where the asymmetrising effect of optically active complexes was employed for the asymmetric synthesis of α-amino-acids. The asymmetric transamination of α-amino-acids in the presence of the copper(II) complex of pyridoxal[31] was mentioned above. It was suggested[31] that a dissymmetric chelate compound is formed and then undergoes stereospecific protonation.

Using the Akabori method[82], Murakami and Takahashi[79–81] achieved the asymmetric synthesis of threonine by the Knoevenagel, reaction involving the condensation of acetaldehyde with the active methylene group of optically active L-[Coen$_2$gly]I$_2$. After the breakdown of the complex reaction products, either optically active threonine with $[\alpha]_D^{13} = +3.84°$ ($c = 2.345$; water) or its 2,4-dinitrophenyl derivative with $[\alpha]_D^{11} = -8.22°$ ($c = 2.34$; 4% aqueous solution of $NaHCO_3$) was isolated. The asymmetric yield of threonine was 8%. Paper chromatography showed that the crude products contained threonine, allothreonine, and glycine in the proportions 7 : 2 : 1.

The condensation of acetaldehyde with glycinatobis-[(−)-propylenediamine]cobalt(III) chloride gave a mixture of threonine, allothreonine, and glycine in the proportions 6.5 : 3 : 0.5. However, the crude threonine in the form of the 2,4-dinitrophenyl derivative (yield 75%) exhibited only weak laevorotation $[\alpha]_D^{11} = -1.2°$ ($c = 5.822$; 4% aqueous solution of $NaHCO_3$). The asymmetric yield of threonine was in this case only about 1%.

Asperger[83] achieved the synthesis of optically active alanine by the coordination of methylaminomalonic acid via both carboxy-groups to the ion (+)-*cis*-α-[Co(LL-αα′-dimethyltriethylenetetramine)Cl$_2$]$^+$ with subsequent decarboxylation of the complex. This gave an alanine complex containing L-alanine with 75% optical purity. However, on liberation from the complex ion and isolation, the L-alanine racemised. Asperger believes that the asymmetrising effect of the complex ion consists in a template action in the coordination of methylaminomalonic acid; the decarboxylation of the optically active complex is stereospecific, leading to the formation of a new dissymmetric centre.

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The studies on the asymmetric synthesis of α-amino-acid examined above demonstrate a rapid increase of interest in this problem. Both asymmetric hydrogenation and condensation methods make it possible to achieve in some cases a high degree of non-enzymic asymmetric synthesis of α-amino-acids. However, systematic studies on this problem are essentially only just beginning and further investigations in this field will be of interest.

So far asymmetric synthesis has been carried out for a restricted number of the simplest α-amino-acids. Therefore it will be very important to develop methods for the asymmetric synthesis of essential α-amino-acids such as tryptophan, lysine, methionine, threonine, etc. The study of the effect of the substrate–catalyst interaction on the optical purity and the configuration of the final product has assumed considerable importance in catalytic asymmetric hydrogenation. The study of the effect of hydrogenation conditions (temperature, pressure, medium) on the degree of asymmetric synthesis is noteworthy, since such conditions can affect not only the magnitude but also the sign of the optical rotation of the hydrogenation products. Interesting results may be obtained in investigations of new types of heterogeneous dissymmetric catalysts. In this connection considerable interest attaches to further investigation of the modification of hydrogenation catalysts by low-molecular optically active substances and also of new complexes of optically active polymers with hydrogenation catalysts, which may serve as models of metal enzymes.

The study of optically active polymers as asymmetrising agents with which the substrate can be linked by bonds of different types—covalent, coordination, salt type, hydrogen bonds, van der Waals forces, electrostatic attraction, etc.—has hardly begun. The progress in synthetic polymer chemistry already permits the preparation of polymeric systems which may serve as simple models of natural enzymes. Probably condensation methods of asymmetric synthesis should yield best results in such systems and much attention must be devoted to the development of such methods. In the study of new procedures for asymmetric synthesis attention must be concentrated on those where the asymmetrising agent is regenerated. Then one may hope that further investigation of the asymmetric synthesis of α-amino-acids and other optically active substances will yield, together with useful practical results, also invaluable information about the nature of enzyme action.

During the preparation of the manuscript for the press several papers on the asymmetric synthesis of α-amino-acids were published. Klabunovskii's monograph[84] contains a number of data on the asymmetric synthesis of α-amino-acids by asymmetric catalytic hydrogenation. The asymmetric synthesis of the monomethyl ester of D-aspartic acid with 98% optical purity is almost stereospecific. It was achieved by Vigneron et al.[85] in the hydrogenation over Raney nickel of the cyclic product of the reaction of (+)-*erythro*-1,2-diphenylethanolamine with dimethyl acetylenedicarboxylate followed by the hydrogenolysis of the reduction product over Pd(OH)$_2$.

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