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ASYMMETRIC SYNTHESIS OF ALANINE BY HYDROGENOLYTIC ASYMMETRIC TRANSAMINATION

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Hydrogenolytic asymmetric transamination between alkyl (R)-phenylglycinate and ethyl pyruvate was studied. The effect of the asymmetric moieties and of the solvents used in the asymmetric synthesis were explained by the substrate-catalyst complex.

Several asymmetric syntheses of α-amino acids from α-keto acids and optically active benzylic amines by catalytic hydrogenation have been reported[1-2]. These asymmetric catalytic hydrogenations could be explained by assuming a substrate-catalyst complex during the hydrogenation[2]. The infrared dichroism[3] of ethyl 2-hydroxyimino-3-phenylpropionate on a palladium metal surface supports the existence of the substrate-catalyst complex.

In the previous study from this laboratory, hydrogenolytic asymmetric transamination between α-keto acids and optically active α-phenylglycine in an aqueous alkaline solution was studied[4]. When (R)-phenylglycine was used as the asymmetric moiety, (R)-amino acid was formed[5]. It was considered that the substrate-catalyst complex was not important in this type of catalytic hydrogenation, because a highly polar aqueous alkaline solution was used as the solvent. However, if the reaction was carried out in organic solvents or preferably by the use of esters of α-keto acid and α-phenylglycine, the substrate-catalyst complex would be formed. The configuration of the resulting amino acid could be predicted by the structure of the substrate-catalyst complex.

In the present study, in order to confirm the prediction, hydrogenolytic asymmetric transamination between ethyl pyruvate and esters of (R)-α-phenylglycine was carried out. The Schiff bases(IIIa,b,c) were catalytically hydrogenated in methanol, ethanol, t-butanol, tetrahydrofuran and benzene. By the use of these sets of reactions, the effects of the solvents and of the asymmetric moieties used were studied. The results indicate that the asymmetric catalytic hydrogenation follows exactly as expected by the hypothesis based on the substrate-catalyst complex. The results are summerized in Table 1.

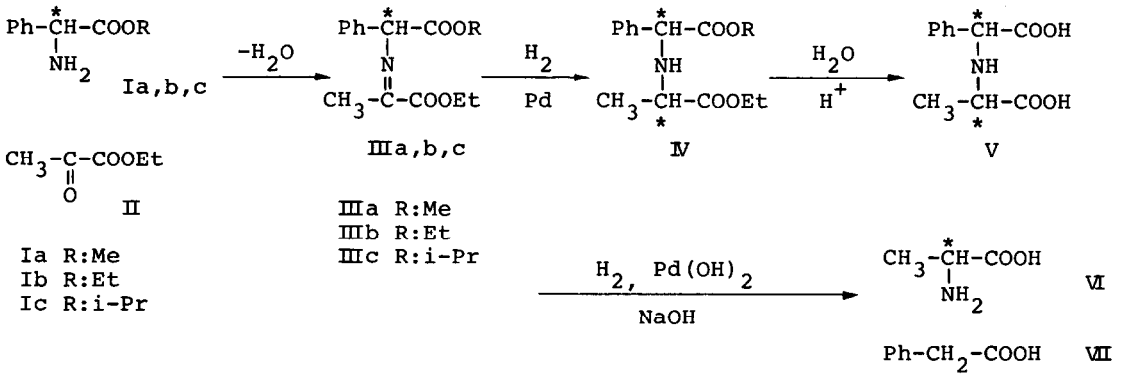


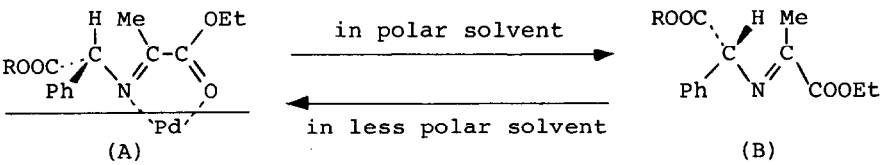
Table 1: Asymmetric synthesis of alanine by hydrogenolytic asymmetric transamination

Asymm. moiety R	Solvent	yield[a] Ala (%)	$[\alpha]_D$ of Ala[b], (c, N HCl)	O.P.[c] (%)	Config. DNP-Ala	$[\alpha]_D$ of DNP-Ala[d] (c, N NaOH)	O.P.[c] (%)
-Me	MeOH	58	+1.4(0.50)	10	S	+13.5(0.75)	9
	EtOH	50	+1.1(0.50)	8	S	+27.5(0.65)	19
	t-BuOH	72	+4.5(0.50)	32	S	+45.3(0.68)	32
	PhH	50	+4.3(0.50)	31	S	+48.3(0.77)	34
-Et	MeOH	60	+0.6(0.51)	4	S	+ 2.6(0.37)	2
	EtOH	62	+1.8(0.50)	13	S	+12.9(0.68)	9
	t-BuOH	38	+1.7(0.51)	12	S	+20.9(1.02)	15
	THF	67	+2.5(0.51)	18	S	+28.3(0.76)	20
	PhH	90	+3.8(1.04)	26	S	+42.3(0.34)	29
-i-Pr	MeOH	56	-2.9(0.52)	20	R	-24.6(0.84)	17
	EtOH	61	-1.5(0.52)	10	R	- 9.8(0.86)	7
	t-BuOH	56	-1.1(0.52)	1	S	+ 6.4(0.79)	4
	PhH	97	+1.3(0.53)	9	S	+20.6(0.83)	14

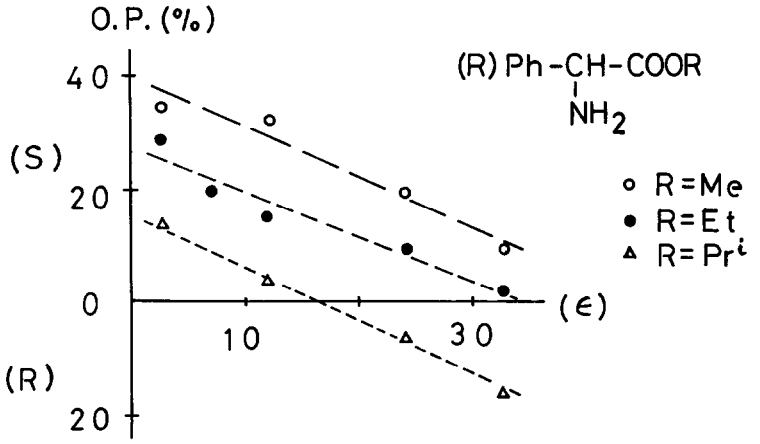
a) The yields are calculated based on ethyl pyruvate.
b) Specific rotations were measured after column separation without further purification.
c) O.P. was defined as $[\alpha]_D$ observed/$[\alpha]_D$ in literature X 100.
d) Specific rotations were measured after column chromatography without further purification.

(R)-Phenylglycine ($[\alpha]_D^{25}$ = -150°, c 1.0, N HCl) was converted to its corresponding methyl, ethyl and isopropyl ester hydrochloride(Ia, Ib, Ic) by thionyl chloride method. ($[\alpha]_D^{25}$: Ia, -134° MeOH; Ib, -115° EtOH; Ic, -91.9° EtOH). The yields of Ia,b,c are in a range of 80 to 90% after recrystallization. Alkyl (R)-phenylglycinate(0.01 mol) and ethyl pyruvate(0.01 mol) were dissolved in 40 ml of dry benzene, and anhydrous sodium sulfate(10 g) was added to the solution to remove the precipitated water and the mixture was kept at room temperature for 24 hr. After filtration and evaporation, the light yellow syrupy Schiff base(IIIa,b,c) was dissolved in 80 ml of methanol and the solution was subjected to catalytic hydrogenation with 0.5 g of 5% palladium on charcoal for

12 hr at room temperature. After hydrogenation, compound(Ⅳ) was hydrolyzed with 20 ml of 6 N hydrochloric acid. The resulting iminodicarboxylic acid(V) was isolated by a Dowex 50 column(Ø 1 cm X 25 cm). This was dissolved in 50 ml of water containing 10 m mol of sodium hydroxide and the solution was hydrogenolyzed using palladium hydroxide on charcoal(1.0 g) for 24 hr at room temperature. After hydrogenation, a part of the solution was diluted appropriately and the yield of alanine was determined by an amino acid analyzer(Yanagimoto model LC-5S). The major part of the solution was acidified and evaporated to dryness and the alanine hydrochloride was extracted with absolute ethanol and free alanine was obtained by the use of a Dowex 50 column. A part of the alanine was treated with 2,4-dinitrofluorobenzene and the resulting DNP-alanine was purified by the use of celite column chromatography using pH 7 citrate-phosphate buffer by eluting with a mixture of chloroform and ether(4 : 1). The yields and the specific rotations of alanine and DNP-alanine are listed in Table 1.



The substrate-catalyst complex could be illustrated as shown above. When the R group of (A) is small(Me), the relative value of the ratio(COOR/Ph) is small. Therefore, the substrate-catalyst complex was hydrogenated from the re face to form (S)-alanine. When the R group becomes larger than the methyl group, the optical purity of alanine would decrease depending on the increase of the bulk of



Dielectric constant(ε): MeOH, 32.7; EtOH, 24.6; Bu^tOH, 12.5; THF, 7.58; PhH, 2.28

Fig 1: Optical purities of DNP-alanine obtained by hydrogenolytic asymmetric transamination by using various solvents

R. Fig 1 shows clearly that the optical purity of alanine is in the order of Me ester > Et ester > i-Pr ester in the substrate(III).

On the other hand, a clear solvent effect in the asymmetric synthesis was observed. The solvents used were benzene, t-buthanol, ethanol and methanol. The relationship between the optical purities and the solvents used is shown in Fig 1. When methyl (R)-phenylglycinate was used as the asymmetric moiety, (S)-alanine was the result(optical purity 34 - 9%). The optical purity of alanine decreased steadily by the use of more polar solvents. When ethyl (R)-phenylglycinate was used, the optical purity of alanine also decreased by the use of more polar solvents(optical purity, 29 - 2%) and the value became almost zero by the use of methanol. In the case of isopropyl (R)-phenylglycinate, the configuration of alanine was inverted by the use of more polar solvents(EtOH, MeOH). These solvent effects could also be explained by assuming the substrate-catalyst complex. When a less polar solvent was used, the attraction between the substrate and the catalyst was stronger, and the substrate-catalyst complex(A) could be formed prior to hydrogenation. However when a polar solvent was used, the attraction between the substrate and the catalyst was weaker and the stronger solvation of the substrate interferred with the formation of substrate-catalyst complex(A). Therefore, in a polar solvent it could be assumed that the amount of the chelated substrate(A) would decrease and the amount of non-chelated substrate(B) would increase. Both structures (A) and (B) would be adsorbed on the catalyst at the less bulky side of the molecule and then hydrogenation would take place. When the configuration of phenylglycinate is (R), (S)- and (R)- alanine are expected to form from structures (A) and (B), respectively. The use of polar solvent increases the population of non-chelated substrate(B), and this would result in the formation of more (R)-alanine. From the results obtained, structure (A) could be the major structure of the substrate in less polar solvents, and structure (B) could be the major conformation of the substrate in ethanol and methanol when isopropyl (R)-phenylglycinate was used.

References and Notes

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5. (R)-α-Methylbenzylamine and (R)-phenylglycine have the same sign in the sequence rule. However, the three dimensional arrangement in space is mirror image each other, if the methyl group is assumed to be equivalent to the carboxy group.