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THE TEMPERATURE DEPENDENCE OF HYDROGENOLYTIC ASYMMETRIC TRANSAMINATION BETWEEN ESTERS OF OPTICALLY ACTIVE PHENYLGLYCINE AND PYRUVIC ACID[1)]

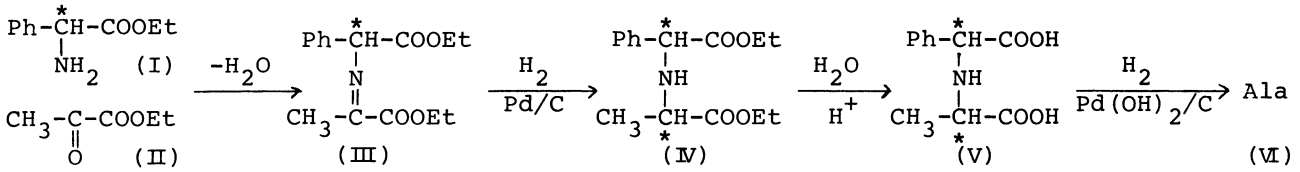
Kaoru HARADA and Yoshiharu KATAOKA
Department of Chemistry, The University of Tsukuba, Niihari, Ibaraki 300-31

Asymmetric synthesis of alanine by hydrogenolytic asymmetric transamination between ethyl (R)-α-phenylglycinate and ethyl pyruvate was studied. Clear temperature dependence in the asymmetric synthesis was observed and the configuration of alanine was inverted depending on the reaction temperature used. The results are explained by the chelation hypothesis based on the substrate-catalyst complex.

Several asymmetric syntheses of α-amino acids from corresponding α-keto acids by hydrogenolytic asymmetric transamination have been reported.[2-5)] In many studies, optically active benzylic amines were used as the asymmetric moieties. In this type of asymmetric synthesis, the configuration and the optical purity of the resulting amino acid could be explained by assuming a substrate-catalyst complex.[3-5)] The infrared dichroism[6)] 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.[7,8)] When (R)-phenylglycine was used as the asymmetric moiety, (R)-amino acid was formed.[9)] It was considered that the substrate-catalyst complex was not important in this 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. The effects of the solvents and the asymmetric moieties in this system were studied and the results indicated that the asymmetric reactions proceed as expected by the chelation hypothesis.[10)]

In the present study, a temperature dependence of the asymmetric catalytic hydrogenation of the Schiff base prepared from ethyl (R)-phenylglycinate and ethyl pyruvate in organic solvents at temperatures between -10～70 °C is described. Ethyl (R)-phenylglycinate(0.01 mol)(I) and ethyl pyruvate(0.01 mol)(II) were dissolved in 30 ml of dry benzene. The mixture was kept standing for 24 h at room temperature. The precipitated water was removed by addition of 10 g of anhydrous sodium sulfate. After separation of sodium sulfate by filtration, the filtrate was evaporated to dryness under reduced pressure. The syrupy light yellow Schiff base(III) was then hydrogenated by the use of 5% palladium on charcoal in methanol(50 ml)(reaction A)



or benzene(50 ml)(reaction B) at various temperatures. After the reaction was over, the catalyst was removed and the solvent was evaporated to dryness. The residual material(Ⅳ) was hydrolyzed with 6 M hydrochloric acid. After evaporation of hydrochloric acid, the resulting iminodicarboxylic acid(V) was isolated by the use of a Dowex 50 column by eluting with 2 M aqueous ammonia. The compound V was then dissolved in water containing two equivalent amount of sodium hydroxide and then hydrogenolyzed with palladium hydroxide on charcoal. After the reaction was over, the catalyst was removed by filtration and the solution was acidified with 6 M hydrochloric acid and the solution was evaporated to dryness under reduced pressure. Alanine hydrochloride was extracted with absolute alcohol and the solution was evaporated to dryness. This was dissolved in a small amount of water and the alanine was isolated by the use of a Dowex 50 column by eluting with 2 M aqueous ammonia. The yield of alanine from ethyl pyruvate is in the range from 50 to 85%. The alanine was converted to DNP-alanine by the use of 2,4-dinitrofluorobenzene. The resulting DNP-alanine was purified by using celite column chromatography[11] using pH 7 citrate-phosphate buffer and by eluting with a mixture of chloroform and ether(2 : 1). The summarized results are shown in Table 1.

The optical purity of alanine was not so high, however, it was found that the

Table 1 Temperature dependence in the asymmetric synthesis of alanine by hydrogenolytic asymmetric transamination by the use of (R)-phenylglycinate(I)

Reaction	Solvent	Temp (°C)	Yield of Ala (%)[a]	Config Ala	$[\alpha]_D$ of DNP-Ala (c, N NaOH)[b]	O.P.[c] (%)
A	MeOH	-10	57	S	+43.5(0.52)	30
		0	63	S	+30.6(0.54)	21
		10	72	S	+23.4(0.53)	16
		20	63	S	+16.4(0.63)	11
		30	85	R	- 1.4(0.56)	1
		40	55	R	- 8.7(0.54)	6
		50	74	R	-19.1(0.56)	13
		60	49	R	-19.6(0.55)	14
B	PhH	30	72	S	+36.7(0.59)	16
		40	58	S	+17.8(0.51)	12
		50	80	S	+ 6.8(0.55)	5
		60	69	S	+ 4.5(0.53)	3
		70	78	R	- 6.9(0.54)	5

a) The yields are calculated based on ethyl pyruvate.

b) Specific rotations were measured after purification by column chromatography.

c) O.P.: Optical purity was defined as $[\alpha]_D$ observed/$[\alpha]_D$ in literature X 100.

configuration of alanine was inverted from S to R depending on the increase of reaction temperature by the use of methanol and also of benzene as the solvent. Figure 1 shows the plot of log R/S against 1/T from the results obtained in the asymmetric reactions. In each set of reactions A and B, the plots are almost linear in the range from -10~70 °C. From these plots, $\Delta\Delta H^{\ddagger}_{R-S}$ and $\Delta\Delta S^{\ddagger}_{R-S}$ of reactions A and B were calulated. Reaction A, $\Delta\Delta H^{\ddagger}_{R-S}$ = -2.3 kcal mol^{-1}, $\Delta\Delta S^{\ddagger}_{R-S}$ = -35.9 cal mol^{-1} deg^{-1}; reaction B, $\Delta\Delta H^{\ddagger}_{R-S}$ = -2.7 kcal mol^{-1}, $\Delta\Delta S^{\ddagger}_{R-S}$ = -39.2 cal mol^{-1} deg^{-1}. These results indicate that the free energy of activation is independent of the reaction temperature.

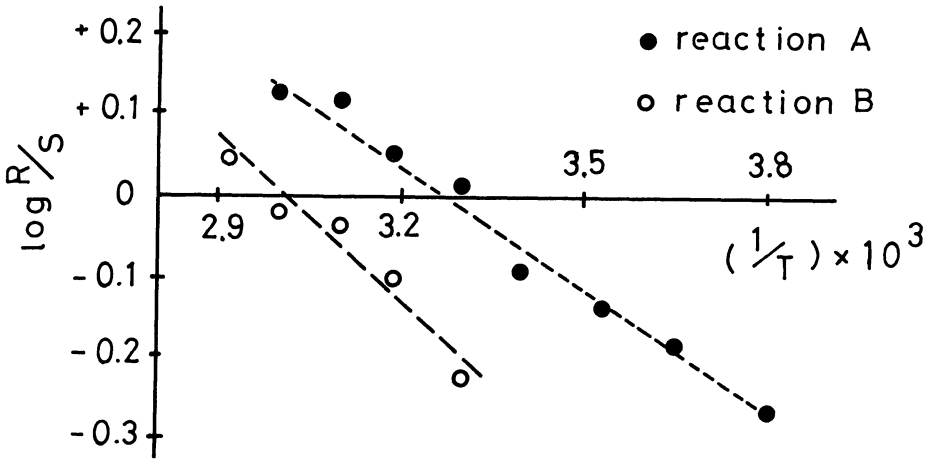
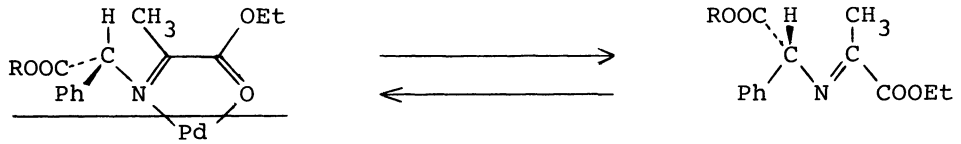


Fig 1: Temperature dependence of hydrogenolytic asymmetric transamination, Reaction A: in methanol; Reaction B: in benzene

The formation of (S)-alanine could be explained by the substrate-catalyst complex as in the previous studies.[3-5] It was considered that the Schiff base(III) first formed intermediate chelated complex IIIa prior to the hydrogenation, and then the substrate was adsorbed at the less bulky side of the chelated molecule and the hydrogenation reaction took place. However, when the reaction temperature rose higher, the chelated complex IIIa was liberated from the palladium sulface to form structure(IIIb) because of the weak interaction between the substrate and the catalyst. Therefore, it could be assumed that the amount of the chelated substrate IIIa descreased depending on the rise of the reaction temperature and the amount of the non-chelated substrate(IIIb) increased. Both structures IIIa, IIIb would be adsorbed at the less bulky side of the molecule and the hydrogenation take place. When the configuration of phenylglycine was R, (S)- and (R)-alanine would be expected from structures IIIa



IIIa

lower temperature

IIIb

higher temperature

and IIIb respectively. Therefore, when a higher reaction temperature was used, the propotion of non-chelated structure IIIb increased and this would result in the formation of more (R)-alanine. From the results obtained, it could be explained that structure IIIa could be the major structure of the substrate at relatively low temperatures in methanol or benzene and structure IIIb could be the major structure of the substrate at higher temperatures. The formation of more (S)-alanine in benzene solution than in methanol at same reaction temperature could be explained also by the intermediate substrate-catalyst complex. The chelated complex IIIa would form more easily in the less polar solvent than in the polar solvent.

The experimental results described here together with the earlier results[10] indicate that the chelation hypothesis is not only applicable to the hydrogenation of Schiff base composed of optically active α-alkylbenzylamine but also applicable to the Schiff base composed of optically active alkyl α-phenylglycinate. This might suggest that the chelation hypothesis could be applied as an empirical general rule in this type of asymmetric hydrogenation reaction.

References and Notes

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