BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 3706—3710 (1972)

Asymmetric Hydrogenation of the C=N Bond. A Study of the Controlling Factors on the Stereoselectivity

Takao YOSHIDA and Kaoru HARADA*

Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka
**Institute for Molecular and Cellular Evolution, University of Miami, Coral Gables, Florida, U. S. A.*

(Received June 24, 1972)

Asymmetric catalytic hydrogenation of Schiff bases, *i. e.*, *N*-(methylbenzylidene)-α-methylbenzylamine and *N*-(ethylbenzylidene)-α-ethylbenzylamine, using 10% palladium hydroxide on charcoal was studied to elucidate the steric course of the reaction. Effects of temperature, solvent, pressure, the amount of the catalyst, and ratio of the *syn* and *anti* isomers on the asymmetric hydrogenation were investigated. Temperature, solvent, the amount of the catalyst were found to be factors which controlled the stereoselectivity of the reaction. The hydrogenation of *N*-(methylbenzylidene)-α-methylbenzylamine always gave a higher asymmetric yield than that of *N*-(ethylbenzylidene)-α-ethylbenzylamine. Lowering the reaction temperature, lowering the polarity of the solvent, and decreasing the amount of the catalyst gave higher stereoselectivities in the hydrogenation reactions.

Studies of the hydrogenolytic asymmetric transamination of Schiff bases between keto acids or their esters and optically active amines have been reported.[1] For the possible steric course of this type of asymmetric hydrogenation, a chelation hypothesis was postulated to explain the experimental results. Solvent and temperature effects were studied to support this hypothesis.[1d,e,f]

Prelog and Scherrer studied the asymmetric hydrogenation of optically active esters of β-methylcinnamic acid.[2] They discussed the relation between the conformations of substrates and the configurations of products. They applied the Prelog rule for the homogeneous reactions to explain the steric course of the heterogeneous hydrogenation. Since there are many other experimental results which can not be explained using the Prelog rule, the mechanism of the hydrogenation reaction was investigated. In order to investigate the reaction mechanism we carried out systematic studies of the asymmetric synthesis in which many parameters of the reaction were examined.

Overberger and his co-workers reported that the asymmetric hydrogenation of (*S*)(−)-*N*-(methylbenzylidene)-α-methylbenzylamine gave a product consisting of 88% (*S,S*) isomer and 12% (*S,R*) isomer.[3] They explained the observed result as follows. "There is a very facile equilibrium between the *syn* and *anti* forms and the *syn* isomer, being a higher energy state, is more easily reduced". However, there is no firm experimental basis for this explanation.

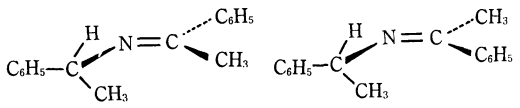

Fig. 1.

In this work *N*-(methylbenzylidene)-α-methylbenzylamine and *N*-(ethylbenzylidene)-α-ethylbenzylamine (I) were used as substrates. Effects of temperature, solvent, pressure, amount of the catalyst, and ratio of the *syn* and *anti* isomers of the substrate on the asymmetric hydrogenation of these substances were investigated.

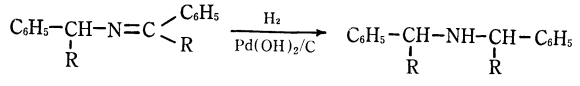

Fig. A.

Results and Discussion

Hydrogenation reactions were carried out using 10% palladium hydroxide on charcoal as a catalyst.

1) a) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961): b) K. Matsumoto and K. Harada, *J. Org. Chem.*, **31**, 1956 (1966): c) K. Harada and K. Matsumoto, *ibid.*, **32**, 1794 (1967): d) K. Harada and K. Matsumoto, *ibid.*, **33**, 4467 (1968): e) K. Harada and T. Yoshida This Bulletin, **43**, 921 (1970): f) K. Harada and T. Yoshida, *Chem. Commun.* **1970**, 1071.

2) V. Prelog and H. Scherrer, *Helv. Chim. Acta*, **42**, 2227 (1959).

3) C. G. Overberger, N. P. Marullo, and R. G. Hiskey, *J. Amer. Chem. Soc.*, **83**, 1374 (1961).

Ratios of two diastereoisomers in the products were determined by gas chromatographic separation using a column packed with 1.5% neopentylglycol succinate on chromosorb-W.

Temperature Effect. Temperature showed marked effect on the hydrogenation reaction. This effect is shown in Table 1 and Fig. 2 in which the percentage of DL isomers is plotted against temperature. As the reaction temperature decreased, the stereoselectivity of the reaction increased from 68% at 50°C to 89% at −20°C when R was CH_3 in I, and from 61% at 50°C to 81% at −20°C when R was C_2H_5 in I. The table shown below indicates the time required for the absorption of the equimolar amount of hydrogen. The rate of the hydrogenation reaction slowed down as the reaction temperature decreased from 30°C to −20°C, but at high temperatures the rate slowed down slightly.

React. temp. (°C)	50	40	30	20	10	0	−10	−20
React. time required (min)	14	10	8	8	10	10	22	60

Solvent Effect. Solvent effects are summarized in Table 2 and Fig. 3.

Pressure Effect. Pressure did not show any significant effect as shown in Table 3. Only a 5% increase in stereoselectivity was observed when the pressure was changed from 1 to 10 atm.

Effect of Amount of Catalyst. The amount of the catalyst was also found to be the one of the factors that controlled stereoselectivity. As the amount of the catalyst decreased, the DL-isomer ratio was increased as shown in Table 4.

Effect of syn-anti *Ratio of Substrate.* It was found that the ratio of the *syn* and *anti* forms of substrates was changed after redistillation. The *syn* and *anti* forms reached an equilibrium if they were allowed to stand for a few days at room temperature. In this experiment the substrates which had different ratios of *syn* and *anti* forms were hydrogenated in methanol and benzene. As shown in Table 5, the ratios of the products were not affected by the *syn* and *anti* ratios of the substrates.

In Table 6 the isomer ratio of the product during the reaction is shown. From the fact that the amine produced did not affect the stereoselectivity of the hydrogenation of the substrate secondarily during the reaction, it appears that the hydrogenated substrate desorbed rapidly from the active surface of the catalyst and exchanged with the unreacted substrate.

Table 1. Temperature effect[a]

Substrate	C_6H_5-C(=N-CH(C_6H_5)-CH_3)-CH_3 (*S*)(−)		C_6H_5-C(=N-CH(C_6H_5)-C_2H_5)-C_2H_5 (±)
Reaction Temp. (°C)	Ratio of (*S*,*S*) to (*S*,*R*)		Ratio of (±) to *meso*
+50	68 : 32[b]	(61 : 39)[c]	61 : 39[b]
+40	70 : 30	(67 : 33)	62 : 38
+30	74 : 26	(46 : 54)	68 : 32
+20	77 : 23	(75 : 25)	70 : 30
+10	81 : 19	(76 : 24)	72 : 28
0	86 : 14	(56 : 44)	75 : 25
−10	87 : 13	(81 : 19)	80 : 20
−20	89 : 11	(88 : 12)	81 : 19

a) Hydrogenation was carried out in methanol under atmospheric pressure.
b) Ratios were determined by the gas chromatographic separation of two diastereoisomers.
c) Ratios were determined by measuring optical rotations of distilled products.

We propose the following reaction mechanism for the hydrogenation of this type of substrate. The substrate is isomerized rapidly by the catalyst bringing about an equilibration of the *syn* and *anti* isomers. Each isomer is then hydrogenated at a different rate from the least hindered side. This mechanism is supported by the fact that the ratio of the *syn* and *anti* isomers of the substrate does not affect the stereoselectivity of the hydrogenation. The conformation of the substrate on the catalyst which was proposed by

Table 2. Solvent effect[a]

Substrate		C_6H_5-C(=N-CH(C_6H_5)-CH_3)-CH_3 (±)	C_6H_5-C(=N-CH(C_6H_5)-CH_3)-CH_3 (±)	C_6H_5-C(=N-CH(C_6H_5)-C_2H_5)-C_2H_5 (±)
Reaction temp. (°C)		10	20	20
Solvent (ε)		Ratio of (±) to *meso*[b]	Ratio of (±) to *meso*[b]	Ratio of (±) to *meso*[b]
Methanol	(32.6)	81 : 19	77 : 23	70 : 30
Ethanol	(24.3)	83 : 17	80 : 20	71 : 29
Propanol	(18.3)	84 : 16	82 : 18	72 : 28
n-Amylalcohol	(13.9)	——	83 : 17	76 : 24
Tetrahydrofuran	(7.6)	——	85 : 15	77 : 23
Ethyl acetate	(6.0)	89 : 11	86 : 14	77 : 23
Benzene	(2.3)	85 : 15	——	——
Dioxane	(2.2)	——	85 : 15	70 : 30

a) Hydrogenation was carried out under atmospheric pressure.
b) Ratios were determined by the gas chromatographic separation of two diastereoisomers.

Table 3. Pressure effect[a]

Substrate (*S*)(−) C_6H_5-C(=N-CH(C_6H_5)-CH_3)-CH_3	
Pressure applied (atm)	Ratio of (*S,S*) to (*S,R*)[b]
10	80 : 20
8	79 : 21
6	79 : 21
4	74 : 26
2	75 : 25
1	75 : 25

a) Hydrogenation was carried out in methanol at 25°C.
b) Ratios were determined by the gas chromatographic separation of two diastereoisomers.

Table 4. Effect of amount of catalyst[a]

Substrate (200 mg) (*S*)(−) C_6H_5-C(=N-CH(C_6H_5)-CH_3)-CH_3	
Catalyst (mg)	Ratio of (*S,S*) to (*S,R*)[b]
200	73 : 27
100	73 : 27
50	76 : 24
30	80 : 20
10	85 : 15

a) Hydrogenation was carried out in methanol at 25°C and under atmospheric pressure.
b) Ratios were determined by the gas chromatographic separation of two diastereoisomers.

Table 5. Effect of *Syn-Anti* ratio of substrate[a]

Substrate (±) C_6H_5-C(=N-CH(C_6H_5)-C_2H_5)-C_2H_5		
Solvent	Ratio of *syn* to *anti* of substrate	Ratio of (±) to *meso* of Product
Methanol	40 : 60[b]	73 : 27[c]
Methanol	52 : 48	73 : 27
Benzene	39 : 61	75 : 25
Benzene	57 : 43	73 : 27

a) Hydrogenation was carried out at 14°C under atmospheric pressure.
b) Ratios were determined by the NMR spectra.
c) Ratios were determined by the gas chromatographic separation of two diastereoisomers.

Overberger *et al.*, as shown in Fig. 1, cannot explain the experimental results obtained in this study. In other words the relatively high stereoselectivity would not be expected from the difference in the bulkiness of the hydrogen and methyl groups. If this is the case the stereoselectivity would increase when the methyl group is replaced by the ethyl group.

On the other hand, if we consider that the most populated conformation is the one in which hydrogen is located on the same plane of C_6H_5–C=N, and the

Table 6. Isomer ratio of product during reaction[a]

Substrate (*S*)(−) C_6H_5-C(=N-CH(C_6H_5)-CH_3)-CH_3	
% of Reaction completed[b]	Ratio of (*S,S*) to (*S,R*)[c]
100	80 : 20
80	81 : 19
57	82 : 18
46	82 : 18
20	82 : 18

a) Hydrogenation was carried out in methanol at 10°C and under atmospheric pressure.
b) The percentages were calculated from the gas chromatographic data.
c) The ratios determined by the gas chromatographic separation of two diastereoisomers.

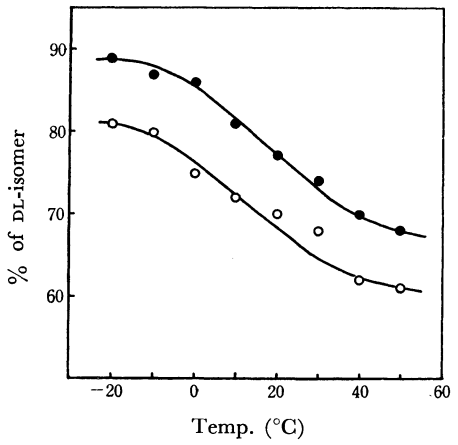

Fig. 2.
—●— C_6H_5-CH(NH-CH(C_6H_5)-CH_3)-CH_3 —○— C_6H_5-CH(NH-CH(C_6H_5)-C_2H_5)-C_2H_5

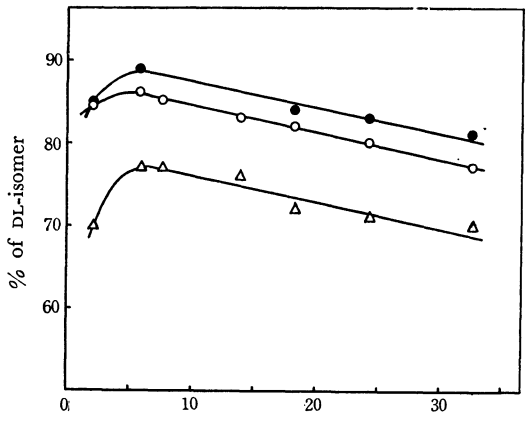

Fig. 3.
—●— (10°C) —△— (20°C) —○— (20°C) C_6H_5-CH(NH-CH(C_6H_5)-C_2H_5)-C_2H_5

anti isomer (II), being a lower energy state, is readily hydrogenated from the least hindered side, that is, from the side of methyl and ethyl group, the difference in bulkiness of methyl (or ethyl) and phenyl group could induce the relatively high stereoselectivity. And also the lowering of stereoselectivity by replacing the methyl with the ethyl group is reasonable when this conformation is considered. This conformation is shown in Fig. 4.

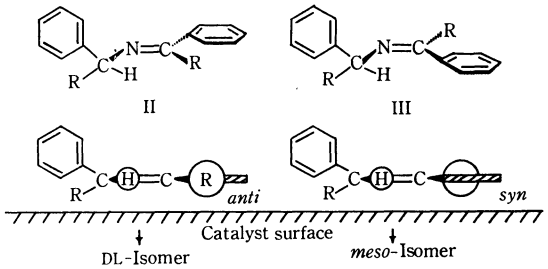

Fig. 4.

Recently the asymmetric reduction of Schiff bases, $R(CH_3)C{=}N{-}CH(CH_3){-}C_6H_5$ (R=Et, *i*-Pr, *t*-Bu), using $LiAlH_4$ and B_2H_6, and also the catalytic reduction using palladium hydroxide on charcoal were reported by Charles *et al.*[4] They discussed the steric course of the reaction and concluded that the conformation of the substrate at the transition state would be the one represented in Fig. 5. Interestingly their proposed substrate conformation on the catalyst is the same as we proposed.

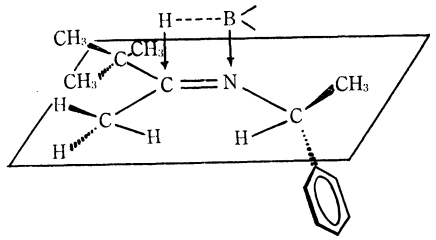

Fig. 5.

The temperature effect could be explained as follows. At low temperature the hydrogenation of the *anti* isomer (II), which is more stable in the preffered conformation, takes place much faster than that of the *syn* isomer (III), thereby resulting in high stereoselectivity. As the temperature increases, the difference of the hydrogenation rate for both isomers becomes smaller resulting in lower stereoselectivity.

The solvent effect could be explained as follows. When a polar solvent was used, the interaction between the solvent and the substrate is stronger and it causes the adsorptive strength of the substrate to be weaker. Therefore it is reasonable that the stereoselectivity of the reaction is lowered in polar solvents. However an increase in the stereoselectivity was not found in the less polar solvents, benzene and dioxane. The strong interaction between the solvent and the catalyst could possibly explain this result.

4) J. P. Charles, H. Christol, and G. Solladie, *Bull. Soc. Chim. Fr.*, **1970**, 4439.

The small effect of pressure is expected for this type of substrate, because the π-electrons of the C=N bond would conjugate with the π-electrons of the phenyl group. The π-benzyl group would then be adsorbed on the surface of the catalyst resulting in fast *cis*-addition of hydrogen.

The effect of the amount of the catalyst could also be rationalized by the competitive adsorption of the substrate. When the amount of catalyst is small, the more reactive *anti* isomer could be adsorbed faster than the *syn* isomer resulting in higher stereoselectivity.

In earlier work we found that solvents and temperatures could affect the stereoselectivity of the asymmetric hydrogenolytic transamination.[1e,f] For the reaction mechanism, it was proposed that two predominant conformations on the catalyst surface were possible, and under certain conditions, one conformation would prevail over the other. Since *N*-(methylbenzylidene)-α-methylbenzylamine and *N*-(ethylbenzylidene)-α-ethylbenzylamine have only one polar group to be hydrogenated, effects of temperatures and solvents could be expected to be smaller than that observed in earlier work.[1e,f] In fact, experimental results showed that these effects were smaller.

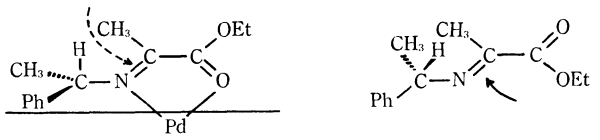

Fig. 6.

We conclude that the factors, which control the stereoselectivity of the asymmetric hydrogenation reaction, are mainly the structure of the molecule, temperature, solvent, and the amount of the catalyst.

Experimental

All melting points are uncorrected. IR and NMR were measured respectively by use of a Jasco IR-S and Varian A-60, T-60.

N-(Methylbenzylidene)-α-methylbenzylamine. This compound was prepared as described by Overberger.[3] bp 104—106°C/0.1 mmHg; (*S*)(−)-isomer, $[\alpha]_D^{25}$ −98.4° (*c* 5.59, benzene).

(S,S)(−)-α,α'-Dimethyldibenzylamine. The same procedure[3] was used to prepare this optically active amine. bp 110°C/1 mmHg $[\alpha]_D^{25}$ −197.3° (*c* 3.65, benzene). The hydrochloride did not melt at temperatures up to 300°C as described in literature. $[\alpha]_D^{25}$ −72.1° (*c* 2.94, ethanol).

N-(Ethylbenzylidene)-α-ethylbenzylamine. This compound was prepared in a similar manner, by using toluene as a solvent with a reaction time of 48 hr. Yield 74%, bp 123—124°C/2 mmHg.

Found: C, 85.57; H, 8.48; N, 5.43%. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57%.

The optically active (*S*)(−)-isomer showed $[\alpha]_D^{25}$ −41.2° (*c* 4.31, benzene).

(S,S)(−)-α,α'-Diethylbenzylamine. (*S*)(−)-*N*-(Ethylbenzylidene)-α-ethylbenzylamine (3.6 g. 0.014 mol) in ethyl acetate (60 m*l*) was hydrogenated at room temperature under atmospheric pressure using 10% palladium hydroxide on charcoal as a catalyst. After one molar amount of

hydrogen was taken up, the catalyst was filtered off. The solvent was removed and the residual oil was distilled *in vacuo*. Yield, 2.7 g (74%), bp 115—118°C/1 mmHg.

Found: C, 84.94; H, 9.13; N, 5.63%. Calcd for $C_{18}H_{23}N$: C, 85.32; H, 9.15; N, 5.53%.

Amine obtained (2.7 g, 0.011 mol) was treated with 50 m*l* of 0.5 N hydrochloric acid to crystallize the hydrochloride. The hydrochloride (2.7 g) was collected and recrystallized from water three times. The pure (*S,S*)(−)-α,α′-diethyldibenzylamine hydrochloride melted at 210.5—211.5°C, $[\alpha]_D^{25}$−66.0 (*c* 1.91, ethanol).

Found: C, 74.55; H, 8.48; N, 4.85; Cl, 12.11%. Calcd for $C_{18}H_{24}NCl$: C, 74.59; H, 8.35; N, 4.83; Cl, 12.23%.

Optically pure (*S,S*)(−)-α,α′-diethyldibenzylamine was recovered from this hydrochloride by decomposition with aqueous sodium hydroxide. $[\alpha]_D^{25}$−203.1° (*c* 2.91, benzene).

Hydrogenation of Schiff Bases. Hydrogenation was carried out in a three-necked round bottom flask provided with a thermometer. Stirring was conducted with using a magnetic stirrer. In every reaction, the 10% palladium hydroxide on charcoal was all from the same lot that was prepared by a method described in the literature.[1)]

Temperature Effect. Schiff base (0.004 mol) in methanol (25 m*l*) was hydrogenated using 200 mg of 10% palladium hydroxide on charcoal under atmospheric pressure. Temperature was controlled by cooling the reaction flask in dry ice-methanol bath or by heating in a water bath. The experimental error of temperature was ±1°C in any reaction. The results obtained are listed in Table 1. The diastereoisomeric ratio of the reaction product was determined by gas chromatography directly instead of measuring the optical rotation of the distilled product to avoid possible fractionation during distillation. In fact the values obtained by the latter method did not correspond to the ones obtained by the gas chromatographic method.

Solvent Effect. Schiff bases (0.004 mol) in various solvents (25 m*l*) were hydrogenated using 200 mg of 10% palladium hydroxide on charcoal at 10° and 20° under atmospheric pressure. The results are listed in Table 2.

Pressure Effect. (*S*)(−)-*N*-(methylbenzylidene)-α-methylbenzylamine (0.002 mole) in methanol (25 m*l*) was hydrogenated using 100 mg of 10% palladium hydroxide on charcoal at 25° in a high pressure durable glass tube using a magnetic stirrer for agitation. The pressure was maintained by connecting the hydrogen cylinder at a fixed pressure to the reaction tube. The decrease of the pressure during reaction by consumption of hydrogen was negligible. The results are listed in Table 3.

Effect of Amount of Catalyst. (*S*)(−)-*N*-(methylbenzylidene)-α-methylbenzylamine (0.001 mol) in methanol (12 m*l*) was hydrogenated using 200, 100, 50, 30, and 10 mg of 10% palladium hydroxide on charcoal respectively at 25°C under atmospheric pressure. The results are listed in Table 4.

Effect of syn-anti *Ratio of Substrate.* (±)-*N*-(Ethylbenzylidene)-α-ethylbenzylamine (0.001 mol) in methanol or benzene (12 m*l*) was hydrogenated using 50 mg of 10% palladium hydroxide on charcoal at 14°C under atmospheric pressure. The ratio of *syn* to *anti* isomers of the substrate was calculated from the NMR spectrum in which the integral of the peaks at δ 4.05 (*syn*) and 4.53 (*anti*) ppm for a methine proton was used. The results are listed in Table 5.

Isomer Ratio of the Product during the Reaction. (*S*)(−)-*N*-(methylbenzylidene)-α-methylbenzylamine (0.004 mol) in methanol was hydrogenated using 200 mg of 10% palladium hydroxide on charcoal at 10°C under atmospheric pressure. The reactions were interrupted when the hydrogen consumption equaled 20, 40, 60, 80, and 100% of the theoretical amounts. The real percentages of the reaction completed were determined by the gas chromatographic method. The results are listed in Table 6.

Gas Chromatographic Separation of Diastereoisomers. The separation of (*S,S*)(−)-or (±)-α,α′-dimethyldibenzylamine from *meso* isomer, and (±)-α,α′-diethyldibenzylamine from *meso* isomer was carried out with the use of Shimadzu GC-3AF. Column length; 3 m, liquid phase; Neopentylglycol succinate 1.5% on Chromosorb-W, Column temperature; 155°C, Retention time; (*S,S*)(−)-and (±)-α,α′-dimethyldibenzylamine- 8.5 min, *meso*-α,α′-dimethyldibenzylamine-9.5 min, (*S,S*)(−)-and (±)-α,α′-diethyldibenzylamine- 8.7 min, *meso*-α,α′-diethyldibenzylamine-9.8 min, *N*-(methylbenzylidene)-α-methylbenzylamine-14.5 min, *N*-(ethylbenzylidene)-α-ethylbenzylamine-11.5 min.

The authors wish to express their thanks to Professor T. Shiba of the Department of Chemistry, Osaka University, for his valuable discussions and suggestions.