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Electrostatic interaction and induced fitting of the rhodium(I) complex coordinated by diphosphine ligand having an amino group in the diastereoselective hydrogenation of dehydrodipeptides

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Abstract

Rhodium(I)–[2-[2-(dimethylamino)ethyl]-1,3-propanediyl]bis(diphenylphosphine) (DPP-AE) catalyst achieved an effective 1,4-asymmetric induction and afforded high diastereoselectivity (max. 96% *d.e.*) in the hydrogenation of dehydrodipeptides in protic solvents. Activation parameters indicate the important role of the electrostatic interaction for the asymmetric induction in the hydrogenation. Structural study of the rhodium(I) DPP-AE complex by ^{31}P NMR and circular dichroism spectroscopies indicated that induced fitting of the complex occurred by the electrostatic interaction between the ligand (DPP-AE) and dehydrodipeptide to change the dominant skew-conformation of the complex according to the chiral center of the substrate. © 1997 Elsevier Science S.A.

Keywords: Asymmetric hydrogenation; Electrostatic interaction; Induced fitting; 1,4-Asymmetric induction; Rhodium catalyst; Dehydrodipeptide

1. Introduction

Catalytic asymmetric hydrogenation of olefinic compounds with transition metal complexes has been studied intensively in the last two decades using many chiral diphosphine ligands [1], and very high enantiomeric excesses (~ 100% *e.e.*) [2] were achieved in the hydrogenation of dehydroamino acid derivatives. In most of these studies, chiral catalysts were designed to conduct asymmetric induction by the steric repulsion between chiral ligand and prochiral substrate. On the other hand, enzymes efficiently use attractive forces, such as electrostatic interaction, hydrogen bonding and van der Waals attractive interaction, in addition to the steric repulsion in their highly stereoselective reactions. Incorporation of such an attractive interaction into a catalytic system will afford multi-site recognition of substrates to facilitate the effective asymmetric induction and will realize synthetic enzymes (chemzyme) [3].

We have reported chiral diphosphinite ligands with an aminoethyl moiety (POP-AE) and the rhodium(I)–POP-AE catalyst achieved very high diastereoselectivities more than 98% *d.e.* in the hydrogenation of dehydrodipeptide (Ac–ΔPhe–(*S*)-Phe–OH) to suggest the possibility of electrostatic interaction between the ligand and the substrate [4]. We also designed an achiral diphosphine ligand with an aminoethyl unit, [2-[2-(dimethylamino)ethyl]-1,3-propanediyl]bis(diphenylphosphine) (DPP-AE), to conduct an electrostatic interaction with dehydrodipeptides, and high stereoselectivities up to 96% *d.e.* were achieved by 1,4-asymmetric induction (Fig. 1) [5,6]. Hayashi et al. reported the high asymmetric induction (max. 97% *e.e.*) in the hydrogenation of acrylic acid derivatives using chiral ferrocenyl diphosphine having an aminoalkyl moiety [7], too.

In this paper, we examine the effect of the electrostatic interaction on the stereoselectivity by estimating activation parameters for hydrogenation of various de-

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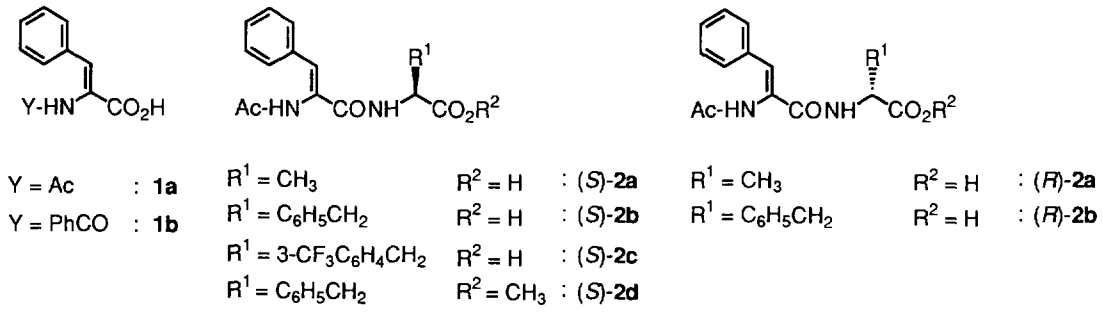


Fig. 1. Dehydroamino acids and dehydrodipeptides.

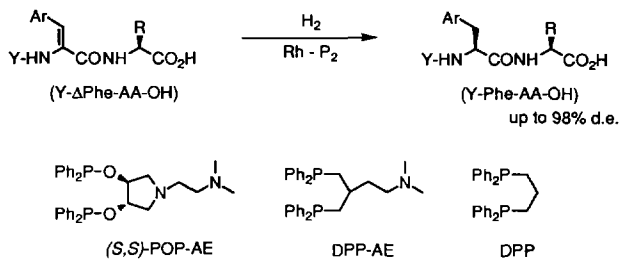
hydrodipeptides and on the conformational change of the rhodium(I)–DPP-AE–substrate complex using NMR and circular dichroism spectroscopies.

2. Results and discussion

The results of asymmetric hydrogenation of dehydrodipeptides (Scheme 1) are shown in Tables 1 and 2. The rhodium(I)–DPP-AE catalyst gave high selectivities in the system where electrostatic interaction is possible, while the rhodium(I)–1,3-bis(diphenylphosphino)propane (DPP) catalyst gave moderate or low selectivities (Table 1).

Different behaviors were observed on changing the reaction temperature, depending on the possibility of the electrostatic interaction. For the systems of DPP-AE–Ac–ΔPhe–AA–OH, the diastereoselectivity increased with raising the temperature to reach a maximum at near room temperature, while DPP-AE–(*S*)-**2d** or DPP–dehydrodipeptides systems indicated only a little change of the selectivity (Table 2).

Differences of the activation enthalpies and activation entropies were estimated from the dependency of the diastereoselectivity on the reaction temperature and are shown in Table 3. The hydrogenation of dehydrodipeptides having a free carboxyl unit by the rhodium(I)–DPP-AE catalyst is characterized by a relatively large positive value of difference of activation entropies $\Delta\Delta S^{\ddagger}$, irrespective of amino acid moiety in the substrate, and $\Delta\Delta G^{\ddagger}$ is governed by the $T\Delta\Delta S^{\ddagger}$ term (Table 3, entries 1–4), while systems not capable



Scheme 1. Asymmetric hydrogenation of dehydrodipeptides by rhodium(I)-complexes.

of the electrostatic interaction between the ligand and the substrate are characterized by small values of $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta G^{\ddagger}$ and are generally governed by the $\Delta\Delta H^{\ddagger}$ term (Table 3, entries 5–10). These results suggest that a large change in the degree of freedom of the complex occurs in the asymmetry-inducing step for the rhodium(I)–DPP-AE–dehydrodipeptide systems capable of the electrostatic interaction between the ligand and the substrate. Provided the change in the electrostatic interaction occurs at the asymmetry-inducing step, it would afford a large entropy change. It is concluded that the electrostatic interaction occurs in the rhodium(I)–DPP-AE–dehydrodipeptide systems to give a large $\Delta\Delta G^{\ddagger}$ governed by $T\Delta\Delta S^{\ddagger}$ and cause an efficient 1,4-asymmetric induction in the hydrogenation.

The structures of the rhodium(I)–DPP-AE and –DPP complexes were examined using ^{31}P NMR and circular dichroism spectroscopies. In ^{31}P NMR in methanol-d_1 of the rhodium(I)–dehydroamino acid (**1a**) complex

Table 1
Effect of solvent polarity on asymmetric hydrogenation of dehydrodipeptides

Entry	Ligand	Substrate	Solvent	Time (h)	Conv. (%)	*d.e.* (%)
1	DPP-AE	(*S*)-**2b**	MeOH–H_2O	48	88	71
2			MeOH	0.5	100	94
3			EtOH	0.8	100	92
4			2-PrOH	1.5	50	56
5		(*S*)-**2c**	MeOH–H_2O	168	100	82
6			MeOH	72	100	95
7			EtOH	144	100	70
8			2-PrOH	281	100	58
9	DPP	(*S*)-**2a**	MeOH	1	80	39
10			EtOH	1	42	47
11			2-PrOH	12	100	39
12		(*S*)-**2b**	MeOH	1	100	34
13			EtOH	1	100	41
14			2-PrOH	12	100	27
15		(*S*)-**2c**	MeOH	19	100	59
16	DPP-AE	(*S*)-**2d**	MeOH	24	34	54
17			2-PrOH	24	73	40

Conditions: P_{H_2} = 0.1 MPa, 20 °C; [Substrate]/[Rh]/[Ligand] = 50/1/1.1; MeOH:H_2O = 2:1 (v/v). Absolute configuration was (*S*,*S*) in all cases. Conversion and %*d.e.* were determined by ^1H NMR spectra.

Table 2
Effect of temperature on asymmetric hydrogenation of dehydrodipeptides [a]

Entry	Ligand	Substrate	Temperature (°C)	Time (h)	Conv. (%)	*d.e.* (%)
1	DPP-AE	(*S*)-**2b**	−60	240	10	35
2			−20	24	100	77
3			0	13	100	89
4			20	0.5	100	94
5			40	1	100	77
6			60	1	100	56
7		(*S*)-**2c**	−37	336	48	82
8			−20	137	70	86
9			0	99	100	90
10			20	72	100	95
11			40	120	100	84
12			60	78	100	81
13	*o*-Tol-DPP-AE	(*S*)-**2b**	−20	168	22	28
14			20	72	95	61
15			60	43	100	30
16 [b]	DPP-AE	(*S*)-**2d**	−20	221	35	63
17 [b]			0	44	100	53
18 [b]			20	24	34	54
19 [b]			40	21	100	55
20 [b]			60	20	100	52
21	DPP	(*S*)-**2b**	−35	48	100	38
22			−20	4	100	36
23			0	2	100	33
24			20	1	100	35
25			40	1	100	32
26			60	1	100	21
27		(*S*)-**2c**	20	75	100	46
28			60	75	100	49
29 [c]			0	48	29	42
30 [c]			20	57	100	40
31 [c]			40	51	100	42
32 [c]			60	57	100	44

Absolute configuration was (*S,S*) in all cases. Conversion and %*d.e.* were determined by ^{1}H NMR spectra. *o*-Tol-DPP-AE: [2-[2-(dimethylamino)ethyl]-1,3-propanediyl]bis[di(2-tolyl)phosphine].
[a] Conditions: $P_{H_2} = 0.1$ MPa; [Substrate]/[Rh]/[Ligand] = 50/1/1.1; solvent: methanol; catalyst precursor: $[Rh(nbd)_2]BF_4$.
[b] Catalyst precursor was $[RhCl(cod)]_2$.
[c] Solvent was ethanol.

$[Rh(DPP)(\mathbf{1a})]BF_4$, two sets of eight-line (two double-doublets) spectra were observed indicating the presence of two diastereomeric species in solution. One double-doublet was observed at about 18 ppm and another was at about 34 ppm (Table 4, entry 1). For $[Rh(DPP\text{-}AE)(\mathbf{1a})]BF_4$, similar two sets of two double-doublets were observed at about 23 and 37 ppm (entry 2). The signals of higher magnetic field correspond to the phos-

Table 3
Activation parameters of asymmetric hydrogenation

Entry	Ligand	Substrate	Solvent	*T* (°C)	$\Delta\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})
1	DPP-AE	(*S*)-**2b**	MeOH	−40 to 20	14	75
2			EtOH	−60 to 20	18	88
3		(*S*)-**2c**	MeOH	−37 to 20	13	74
4	*o*-Tol-DPP-AE	(*S*)-**2b**	MeOH	−20 to 40	12	56
5	DPP	(*S*)-**2b**	MeOH	−35 to 40	−1.0	2.5
6		(*S*)-**2c**	EtOH	0 to 60	0.9	10
7 [a]	(*R*)-Prophos	**1b**	BuOH	10 to 80	−7.9	−3.4
8 [a]	(*R*)-Cycphos	**1b**	BuOH	10 to 80	−6.7	2.8
9 [a]	(*S,S*)-Skewphos	**1a**	EtOH	−20 to 70	−12	−8.4
10 [a]	(*R,R*)-DIOP	**1a**	EtOH	25 to 100	−11	−16

(*R*)-Prophos, (*R*)-Cycphos, see Ref. [8]. (*S,S*)-Skewphos, see Ref. [9]. (*R,R*)-DIOP, see Ref. [10].
[a] Activation parameters were estimated from the data reported, Refs. [8–10].

Table 4
^{31}P NMR spectral data of rhodium(I)–diphosphine complexes

Entry	Rh complex		Ratio [a]	δP(1)	δP(2)	$J_{Rh-P(1)}$	$J_{Rh-P(2)}$	$J_{P(1)-P(2)}$
	Diphosphine	Substrate		(ppm)	(ppm)	(Hz)	(Hz)	(Hz)
1	DPP	**1a**	1	18.2	34.1	131	145	48
			1	17.5	34.3	131	145	51
2	DPP-AE	**1a**	1	22.5	37.0	132	144	49
			1	22.7	37.1	132	144	49
3	DPP	(*S*)-**2a**	1	18.0	34.1	134	144	54
			3	18.0	33.6	134	144	54
			3	17.6	34.0	129	144	48
			1	18.2	33.8	131	144	48
4	DPP-AE	(*S*)-**2a**	— [b]	18.5	33.1	112	118	54

[a] Ratio of integrated value for isomeric rhodium complexes.
[b] One species was much amplified and other species were hidden in the background.

phorus atom trans to the olefinic bond and the lower signals correspond to the phosphorus atom trans to the amido carbonyl, and their chemical shifts and coupling constants coincide well with those of rhodium(I)–diphosphine–dehydroamino acid complexes [11]. The six-membered chelate ring exists in an equilibrium between λ- and δ-skew conformations [12]. So, the combination of prochiral faces of dehydroamino acid and skew conformations affords two diastereomeric rhodium species thus showing two sets of two double-doublets. For rhodium(I)–dehydrodipeptide complexes, the chemical shifts and coupling constants of rhodium(I)–DPP and rhodium(I)–DPP-AE complexes were similar to those found for dehydroamino acid complexes (Table 4). This indicates that dehydrodipeptide (**2a**) coordinates to the rhodium by a similar mode to that of dehydroamino acid (**1a**) (Fig. 2). The ^{31}P signals of [Rh(DPP)((*S*)-**2a**)]BF_4 clearly showed the presence of four isomeric species (Table 4, entry 3). The intensity ratio of the signals indicates that no specific species is much stabilized. In the case of the [Rh(DPP-AE)((*S*)-**2a**)]BF_4 system, however, one species was much amplified among four possible complexes and this indicates the large shift of the equilibrium between the four isomeric complexes (Table 4, entry 4). This shift of the equilibrium between isomeric complexes can be ascribed to the effect of the electrostatic interaction between DPP-AE and dehydrodipeptide to change the stability of the one specific complex.

Circular dichroism spectra will afford information on the equilibrium between two skew conformations of the rhodium(I)–DPP-AE–dehydrodipeptide species. The [Rh(DPP-AE)(Ac–ΔPhe–(*S*)-AA–OH)]BF_4 complexes afforded a clear negative Cotton effect at about 400–420 nm, while when using dehydrodipeptides having an (*R*)-chiral center an antipodal Cotton effect [1] was observed for the rhodium(I)–DPP-AE–dehydrodipeptide complexes (Fig. 3(a) and Fig. 3(b)). The rhodium(I)–DPP–dehydrodipeptide ((*S*)-**2a** and (*S*)-**2b**) complexes indicated no significant Cotton effect in spite of the presence of the chiral center in the substrate (Fig. 3(c)). These results indicate that the equilibrium between the λ- and δ-skew conformations of the rhodium(I) species is shifted by the electrostatic interaction between DPP-AE and dehydrodipeptides having a chiral center, reflecting the absolute configuration of the chiral carbon. In the absence of the electrostatic interaction, the λ- and δ-skew are in nearly equal amounts in solution. The rhodium–(*S*,*S*)-Skewphos (chiral 1,3-diphosphine) complex has been reported to indicate a positive Cotton effect at 380–420 nm and to have the δ-skew conformation [13]. By comparing the circular dichroism spectra of the DPP-AE system with that of the (*S*,*S*)-Skewphos complex, we have concluded that the δ-skew conformation becomes dominant for rhodium(I)–DPP-AE–(*R*)-dehydrodipeptide complexes and the λ-skew for the (*S*)-substrate (Fig. 4). Thus, by the electrostatic interaction between the ligand DPP-AE and the dehydrodipeptide, induced fitting occurred corresponding to the absolute configuration of the chiral center in the substrate.

In this hydrogenation system of dehydrodipeptides

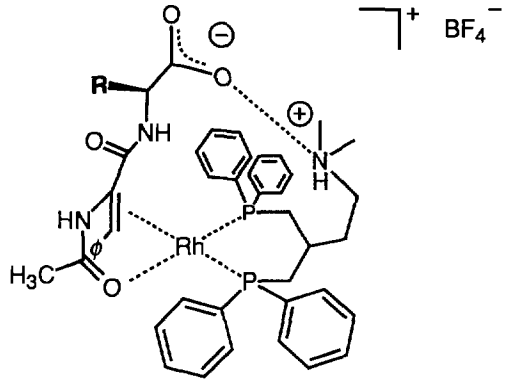


Fig. 2. Supposed structure of rhodium(I)–DPP-AE—dehydrodipeptide complex.

[1] The antipodal Cotton effect was not exactly symmetric to that observed for (*S*)-dehydrodipeptide because of the difficulties in the preparation of samples with an exactly same composition.

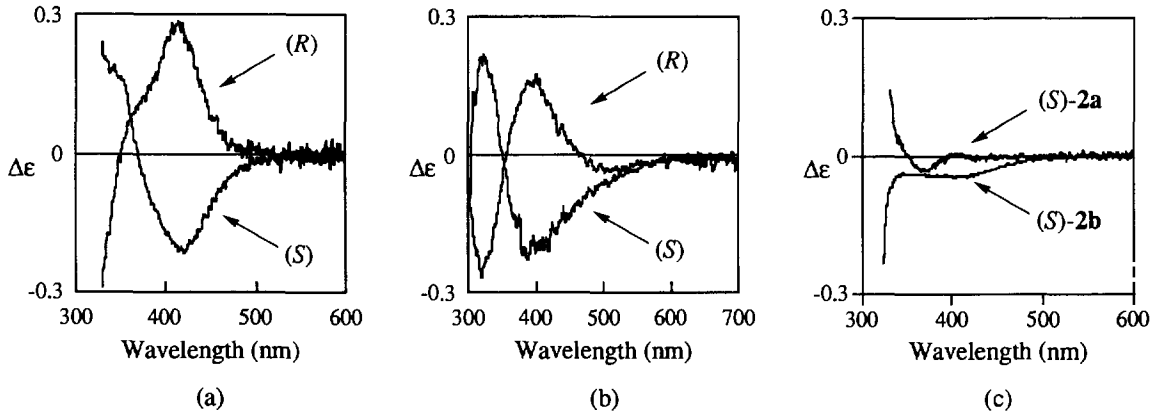


Fig. 3. Circular dichroism spectra of rhodium(I)–diphosphine–dehydrodipeptide complexes. (a) DPP-AE–(*S*)-**2a** and –(*R*)-**2a**, (b) DPP-AE–(*S*)-**2b** and –(*R*)-**2b**, (c) DPP–(*S*)-**2a** and –(*S*)-**2b**.

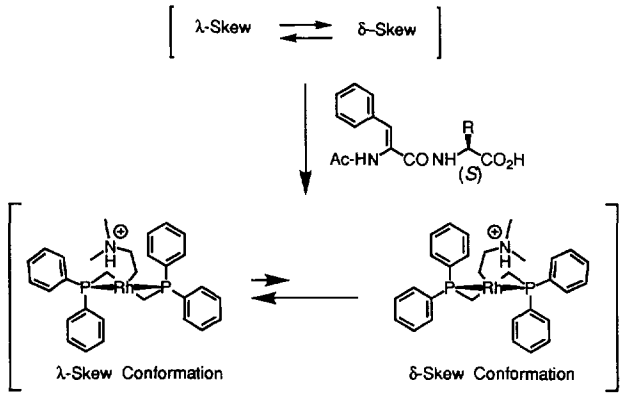


Fig. 4. Induced fitting by electrostatic interaction between DPP-AE and (*S*)-dehydrodipeptide (dehydrodipeptide anion is omitted).

by the rhodium(I)–DPP-AE catalyst, the step determining the asymmetry is not specified yet. However, the electrostatic interaction between the ligand and the substrate plays an important role to recognize the structure of substrates and to cause an effective 1,4-asymmetric induction. Through the electrostatic interaction with dehydrodipeptides having a chiral center, the induced fitting of the rhodium(I)–DPP-AE complex occurs by changing the dominant conformation of the complex and the achiral rhodium(I)–DPP-AE complex behaves like a chiral catalyst to afford high stereoselectivity.

3. Experimental

^{1}H NMR spectra were recorded with a JEOL EX-270 spectrometer with tetramethylsilane as internal standard. ^{31}P NMR spectra were recorded with JEOL EX-270 and EX-400 spectrometers in CH_3OD, with 85% H_3PO_4 as external standard.

3.1. Dehydrodipeptides synthesis

The *N*-acethyldehydrophenylalanyl-amino acids were prepared from dehydrophenylalanine azlactone and the corresponding chiral amino acids according to the method by Bergmann and coworkers [14].

3.2. Asymmetric hydrogenation

The catalyst solution, prepared from $[Rh(nbd)_2]BF_4$ or $[RhCl(cod)]_2$ and the diphosphine ligand in absolute alcohol, was transferred with a fine stainless tube to the hydrogenation vessel containing dehydrodipeptide. The substrate–catalyst solution was stirred under nitrogen for 1 h, and then hydrogen gas was introduced. The reaction was followed by monitoring the amount of hydrogen consumed at regulated temperature. After the reaction, the rhodium catalyst was removed with DOWEX 50 cation-exchange resin and dipeptides were converted into methyl ester in methanol-thionyl chloride. The diastereomeric excess was determined by ^{1}H NMR method in the presence of $Eu(fod)_3$ integrating the signal of the diastereotopic methyl protons of the ester unit of the *N*-protected dipeptides [15].

3.3. ^{31}P NMR and circular dichroism spectra

The solution of $[Rh(nbd)_2]BF_4$, a diphosphine and a substrate in methanol (CH_3OD or CH_3OH) in a Schlenk tube was degassed by a freeze and thaw cycle. Hydrogen gas was introduced and the solution was stirred at 5 °C for the time necessary for removing the coordinated bicyclo[2.2.1]hepta-2,5-diene. Then the solution was evacuated by three freeze and thaw cycles, transferred into an NMR tube or the 10 mm circular dichroism cell, and sealed under nitrogen.

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