^{31}P-Nuclear Magnetic Resonance Studies on Various *N*-Substituted Pyrrolidinebisphosphine–Rhodium Complexes to Clarify the *N*-Substituent Effect on Catalytic Asymmetric Hydrogenation[1)]

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The *N*-substituent effect on the enantioselectivity and the catalytic activity of the rhodium complexes of pyrrolidinebisphosphine ligands, PPMs and CPMs, was examined by means of hydrogenation studies and ^{31}P-nuclear magnetic resonance spectral analysis.

Keywords ^{31}P-NMR; rhodium–bisphosphine complex; *N*-substituted pyrrolidinebisphosphine; catalytic asymmetric hydrogenation; 2-methylene succinamic acid; phenacylamine derivative

We have reported several efficient chiral bisphosphine ligands for rhodium-catalyzed asymmetric hydrogenation.[2)] Almost all of them in recent years were designed on the basis of our concept that one phosphino group plays an important role in the enantioselectivity and the other does so in the catalytic activity. BCPM[3)] ((2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-(dicyclohexylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine) was developed by a modification of BPPM[4)] ((2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine) on the basis of this concept. As a next step, we are interested in the effects of the *N*-substituent on the pyrrolidinebisphosphine, with the goal of increasing both the enantioselectivity and the catalytic activity of the rhodium complex. All of the *N*-substituted PPMs and CPMs discussed here are listed in Chart 1. Several *N*-acyl and *N*-alkoxycarbonyl PPM analogues have been prepared to find the optimum ligand for the asymmetric hydrogenation of itaconic acid.[5)] Moreover, *N*-carbamoyl PPMs were also synthesized recently and found to be superior to other *N*-substituted PPMs.[6)] In the cases of various CPMs–rhodium complexes too, *N*-carbamoyl analogues gave better results than the others.[7)]

Table I shows the results of the asymmetric hydrogenation of 2-methylene succinamic acid catalyzed by various PPM–rhodium complexes.[6)] This compound can be led to optically active γ-butyrolactone. When the hydrogenations were taken to completion, there were no significant differences among the enantioselectivities of these complexes. But at a lower hydrogen pressure (1 atm), the rhodium complexes of *N*-carbamoyl PPM could complete the hydrogenation with higher enantioselectivity (75—77% ee).

Similar results were obtained in the asymmetric hydrogenation of a phenacylamine derivative catalyzed by rhodium complexes of CPM analogues, as shown in Table II.[7a)] This prochiral aminoketone is a good precursor of optically active phenylephrine. The rhodium complex of MCCPM which bears an *N*-carbamoyl group could achieve moderately better optical yields than the others. MCCPM was found to be a potentially good ligand even in asymmetric hydrogenation of the other aminoketones.[7b)]

In order to clarify the effect of the *N*-carbamoyl group, we conducted ^{31}P-nuclear magnetic resonance (NMR) studies of the rhodium complexes, and typical proton-decoupled spectra of [Rh(COD)·bisphosphine]$^+$ClO$_4^-$ are shown in Figs. 1 and 2. The rhodium complexes were prepared *in situ* by mixing [Rh(COD)$_2$]$^+$ClO$_4^-$ and equimolar bisphosphine ligand in methanol-d_4 under an argon atmosphere at 25 °C with 85% H_3PO_4 as an external standard.

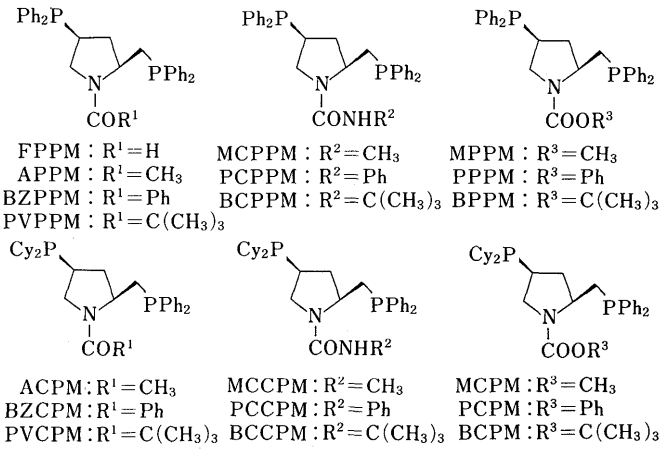
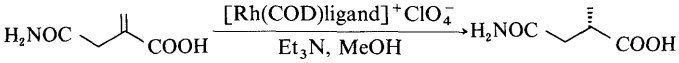


Chart 1. *N*-Substituted PPMs and CPMs

TABLE I. Asymmetric Hydrogenation of 2-Methylenesuccinamic Acid[a)]

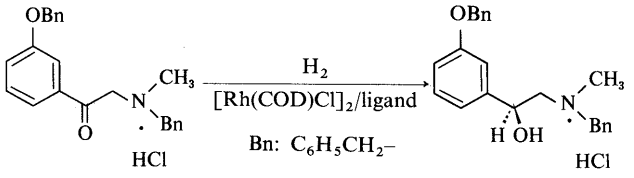


	Ligand	[Subst.]/[Rh]	Convn. %	atm/h	% ee
1	FPPM	100	100	30/20	64
2	FPPM	100	13	5/20	43
3	APPM	100	100	30/20	61
4	BZPPM	100	100	30/20	63
5	PVPPM	100	100	30/20	48
6	MCPPM	1000	82	30/20	59
7	MCPPM	100	100	30/20	65
8	MCPPM	100	100	5/20	70
9	MCPPM	100	100	1/40	75
10	PCPPM	1000	80	30/20	62
11	PCPPM	100	100	30/20	66
12	PCPPM	100	100	5/20	71
13	PCPPM	100	100	1/40	77
14	BCPPM	100	100	30/20	64
15	MPPM	100	100	30/20	66
16	PPPM	100	100	32/20	59
17	BPPM	1000	22	30/20	53
18	BPPM	100	100	30/20	60
19	BPPM	100	5	30/20	—
20	BCPM	1000	Trace	30/20	—

a) Ref. 6.

We have previously suggested that two rotational isomers of the *N*-substituent exist in solution, one with the substituent of the carbonyl group (=NCO–R) *anti* to the pyrrolidine C_2 carbon and the other with it *syn*[8] (Chart 2). In the case of BPPM–rhodium complex, these isomers were observed in almost equal ratio on the ^{31}P-NMR chart (Fig. 1).

TABLE II. Asymmetric Hydrogenation of 3′-Benzyloxy-2-(*N*-benzyl, *N*-methyl)amino Acetophenone Hydrochloride[a]



Entry	Ligand	Product		
		$[\alpha]_D^{23}$ (c=2.0, H_2O)	% ee	Confign.
1	BCPM	+33.8°	75	(*S*)
2	BCCPM	+34.5°	76	(*S*)
3	PVCPM	+34.1°	75	(*S*)
4	PCPM	+32.4°	72	(*S*)
5	PCCPM	+33.6°	74	(*S*)
6	BZCPM	+34.1°	75	(*S*)
7	MCPM	+38.2°	85	(*S*)
8	MCCPM	+38.5°	85	(*S*)
9	ACPM	+35.5°	79	(*S*)

a) [Subst.]/[Rh]=1000, H_2 20 atm/50°C/20 h, ref. 7c.

It can be presumed that they have both different P_1–Rh–P_2 angles and different distances between the metal and the phosphines (Rh–P), *i.e.*, two species with different conformations of the 7-membered chelate ring are considered to exist in solution. For example, the rhodium complex of APPM, one of the *N*-acyl PPMs, also gave higher- and lower-field signals in almost 3:1 ratio. In the case of FPPM bearing an *N*-formyl group, the lower-field signals were more intense and the ratio was almost 1:2. Thus the *N*-substituents remarkably affected the ratio of the isomers. But in the case of MCPPM, one of the *N*-carbamoyl PPMs, only two of four peaks due to the coupling between phosphine atoms ($J_{P_1-P_2}$) and between

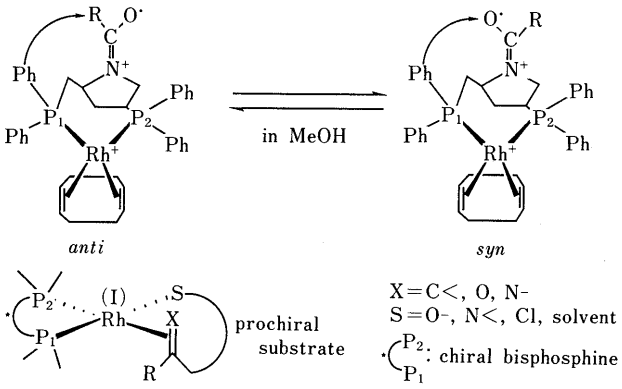


Chart 2

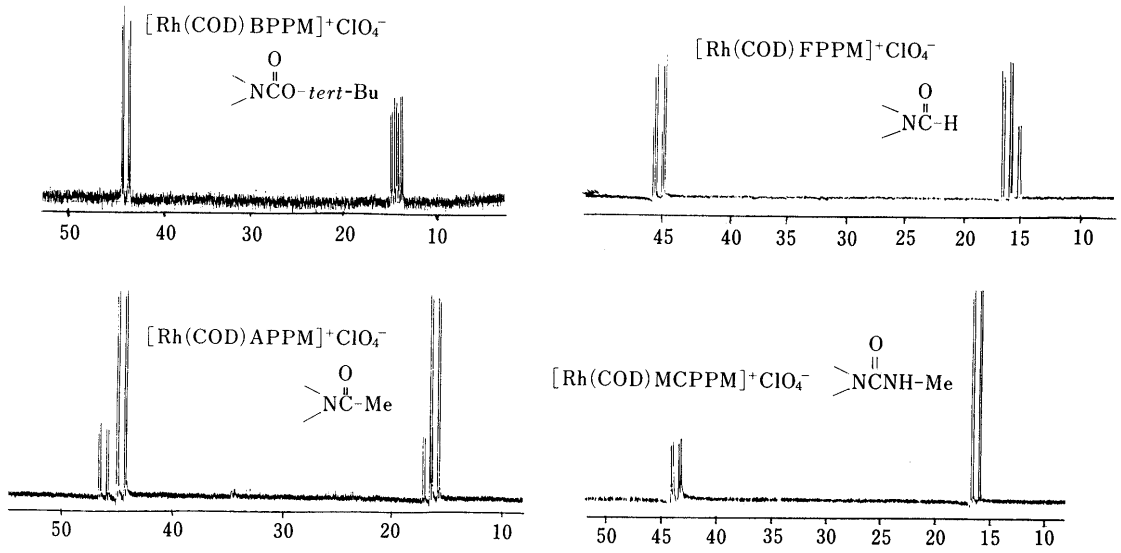


Fig. 1. ^{31}P-NMR Spectra of Cationic Rhodium–PPM Complexes

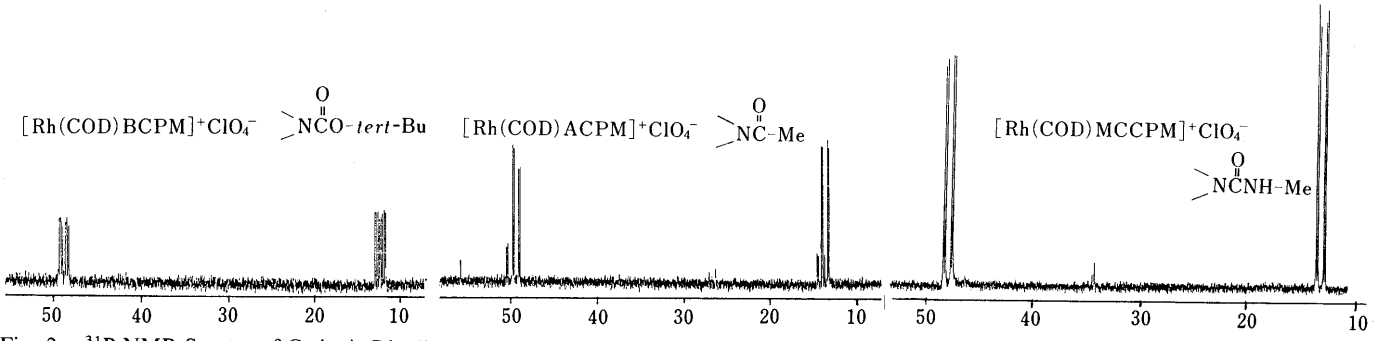


Fig. 2. ^{31}P-NMR Spectra of Cationic Rhodium–CPM Complexes

TABLE III. ^{31}P-NMR Spectral Data for [Rh(COD)·bisphosphine]$^+$ ClO_4^- (PPMs)

Ligand		ppm	J_{Rh-P}	$J_{P_1-P_2}$
MCPPM	P_1	16.4	140.2	38.1
	P_2	43.7	145.0	38.1
PCPPM	P_1	16.4	140.2	37.2
	P_2	43.9	145.0	
BCPPM	P_1	14.9	139.2	37.2
	P_2	43.5	145.0	37.2
FPPM	P_1(A)	15.4	141.2	36.2
	P_2(A)	45.4	145.0	36.2
	P_1(B)	16.2	141.2	37.2
	P_2(B)	45.2	145.0	37.2
APPM	P_1 (A)	16.1	141.1	38.1
	P_2 (A)	45.4	145.0	37.2
	P_1 (B)	16.7	142.0	38.1
	P_2 (B)	46.2	145.0	38.1
BZPPM	P_1	14.1	140.2	36.2
	P_2	45.2	145.9	36.2
PVPPM	P_1	13.7	142.1	—[a]
	P_2	44.9	145.0	—[a]
MPPM	P_1 (A)	16.0	140.7	37.2
	P_2 (A)	43.7	144.0	37.2
	P_1 (B)	16.2	141.1	38.2
	P_2 (B)	46.2	145.0	38.2
PPPM	P_1 (A)	15.2	140.2	37.2
	P_2 (A)	43.6	145.0	37.2
	P_1 (B)	15.3	140.2	37.2
	P_2 (B)	44.6	145.0	37.2
BPPM	P_1 (A)	14.21	139.2	36.2
	P_2 (A)	43.61	145.0	36.2
	P_1 (B)	14.64	140.2	37.2
	P_2 (B)	43.61	145.0	36.2

a) Broad peaks.

TABLE IV. ^{31}P-NMR Spectral Data for [Rh(COD)·bisphosphine]$^+$ ClO_4^- (CPMs)

Ligand		ppm	J_{Rh-P}	$J_{P_1-P_2}$
MCCPM	P_1	13.84	142.1	34.3
	P_2	48.12	137.3	34.3
PCCPM	P_1	13.81	142.7	—[a]
	P_2	48.11	130.0	34.3
BCCPM	P_1	12.96	142.6	34.1
	P_2	48.23	136.9	34.1
ACPM	P_1 (A)	13.56	143.05	33.4
	P_2 (A)	49.42	137.8	33.4
	P_1 (B)	14.02	145.0	33.4
	P_2 (B)	50.11	138.8	33.4
BZCPM	P_1	12.03	143.1	33.4
	P_2	51.56	137.3	33.4
PVCPM	P_1	11.90	152.6	—[a]
	P_2	50.92	138.6	34.3
MCPM	P_1 (A)	13.4	143.1	33.4
	P_2 (A)	48.47	136.4	33.4
	P_1 (B)	13.48	143.1	33.4
	P_2 (B)	48.47	136.4	33.4
BCPM	P_1 (A)	12.18	142.1	33.4
	P_2 (A)	48.71	138.3	33.4
	P_1 (B)	12.56	142.1	33.4
	P_2 (B)	48.95	136.4	33.4

a) Broad peaks.

rhodium and phosphine atoms (J_{Rh-P_1}, J_{Rh-P_2}) were observed predominantly and the signals of P_1 appeared at rather lower field. This means that MCPPM–rhodium complex exists as almost a single species at room temperature in methanol and the phosphino group of P_1 was not so strongly influenced by the carbonyl group of the *N*-substituent. Other rhodium complexes of *N*-carbamoyl PPMs were also observed as single isomers. It is important for efficient catalytic asymmetric reactions that a single active species should exist preferentially in the system. It can be assumed that rhodium complexes of *N*-carbamoyl PPMs were better catalysts than the others for this reason.

Among the rhodium complexes of CPM analogues (Fig. 2), the rhodium complex of MCCPM, one of the *N*-carbamoyl CPMs, also existed as a single species in solution, even though two isomers appeared in the BCPM–rhodium complex solution. In the cases of the rhodium complexes of CPMs, *N*-carbamoyl groups were also found to be good substituents in that a single stable species of catalyst was favored, in accordance with the hydrogenation results.

From the standpoint of our design concept, these ^{31}P-NMR spectral analyses had interesting implications. As the two phenyl rings on the P_1 atom oriented *cis* to the prochiral group (Chart 2) are considered to play important roles in the enantioselection, it is thought to be preferable for enantioselective catalysts that this phosphine atom should appear in the ^{31}P-NMR spectra as a single species showing sharp peaks. All of the rhodium complexes of *N*-carbamoyl PPMs and CPMs show sharp peaks of the P_1 atom in their spectra, so a good chiral environment of the two phenyl groups of the P_1 atom is presumed to exist, favoring enantioselective asymmetric hydrogenation.

In summary, both the enantioselectivity and the activity of the catalyst could be changed considerably by changing the *N*-substituent, and the ^{31}P-NMR studies of these complexes revealed that the substitution of *N*-carbamoyl groups could generate predominantly one conformer of the catalyst in solution at room temperature, resulting in superior enantioselective asymmetric hydrogenation.

Experimental

^{31}P-NMR spectra were taken on a JEOL JNM-GX500 spectrometer (^{31}P, 202.35 MHz) using 85% H_3PO_4 as an external standard. The samples were prepared by mixing 0.01 mmol of $[Rh(COD)_2]^+ClO_4^-$ and 0.01 mmol of the ligands in 0.3 ml of methanol-d_4 under argon at room temperature. Chemical shifts and coupling constants are summarized in Tables III and IV.

References

1) Asymmetric Reactions Catalyzed by Chiral Metal Complexes. XLVII.
2) T. Morimoto, H. Takahashi, K. Fujii, M. Chiba, and K. Achiwa, *Chem. Lett.*, **1986**, 2061; T. Morimoto, M. Chiba, and K. Achiwa, *Tetrahedron Lett.*, **29**, 4755 (1988); K. Inoguchi, T. Morimoto, and K. Achiwa, *J. Organomet. Chem.*, **370**, C9 (1989); T. Morimoto, M. Chiba, and K. Achiwa, *Tetrahedron Lett.*, **30**, 735 (1989).
3) H. Takahashi, M. Hattori, M. Chiba, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **27**, 4477 (1986).
4) K. Achiwa, *J. Am. Chem. Soc.*, **98**, 8265 (1976).
5) K. Achiwa, *Chem. Lett.*, **1978**, 561.
6) H. Takeda, T. Tachinami, S. Hosokawa, M. Aburatani, K. Inoguchi, and K. Achiwa, *Chem. Pharm. Bull.*, **39**, 2706 (1991).
7) *a*) H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **30**, 367 (1989); *b*) H. Takahashi, S. Sakuraba, H. Takeda, and K. Achiwa, *J. Am. Chem. Soc.*, **112**, 5786 (1990); *c*) H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, and K. Achiwa, *Tetrahedron Lett.*, **30**, 363 (1989).
8) K. Achiwa, Y. Ohga, and Y. Iitaka, *Chem. Lett.*, **1979**, 865.