# NAD(P)H-NAD(P)+ Models. 73. Structure-Stereochemistry Relationship in the Reaction of NAD Analog

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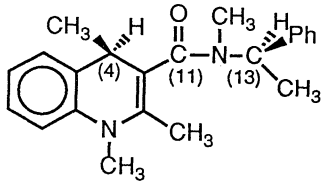
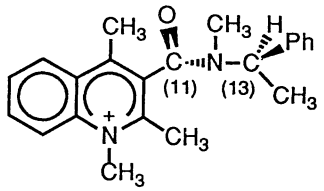
Four different NAD(P)H analogs have been oxidized by various substituted and unsubstituted 1,4-benzoquinones in the presence or absence of magnesium ion. The stereospecificity of the reaction depends not only on the reactivity of quinone but also on that of the analogs as well as on the presence or absence of magnesium ion. The results are discussed from the viewpoint of reaction mechanism for the transfer of a (net) hydride ion.

The central chirality at the $C_4$-position in 3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1,2,4-trimethyl-1,4-dihydroquinoline ($Me_3MQPH$) is converted into the axial chirality with respect to the $C_3$–$C_{carbonyl}$ bond in 3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1,2,4-trimethylquinolinium ion ($Me_3MQP^+$) on oxidation.[1] Stereospecificity of the chirality-transformation depends on the reactivity of the oxidizing reagent.[2,3] It is also known that the reverse reaction proceeds with high stereospecificity under appropriate reaction conditions.[4] However, the structure–stereochemistry, or the reactivity–stereochemistry, relationship in the compounds that undergo the chirality-transformation has not yet been studied, because the compound available for the investigation is limited.

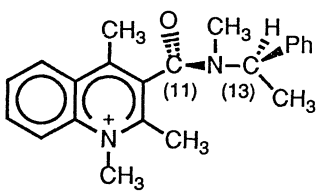
Recently, we found that the axial chirality in 3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethylpyridinium ion ($Me_3PNP^+$) in a nonpolar solvent is reasonably stable at room temperature and the stereospecific conversion of the central chirality in 3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethyl-1,4-dihydropyridine ($Me_3PNPH$) into the corresponding axial chirality in $Me_3PNP^+$ can be studied by means of $^1H$ NMR spectroscopy. 4-Deuteriated $Me_3MQPH$ and $Me_3PNPH$ ($Me_3MQPD$ and $Me_3PNPD$, respectively) are other substrates to be studied. Having four substrates in hand, we thus studied the stereospecificity associated with the chirality-transformation from the viewpoint of the structure–stereochemistry, or the reactivity–stereochemistry, relationship. The results will be discussed in relation to the mechanism of the (net) hydride transfer.



(4*R*,13*R*)-$Me_3MQPH$



(11*R*,13*R*)-$Me_3MQP^+$



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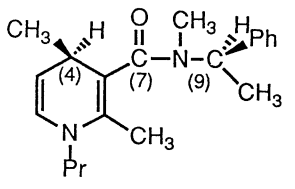

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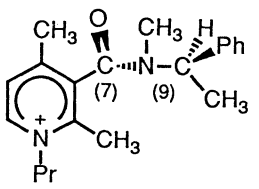

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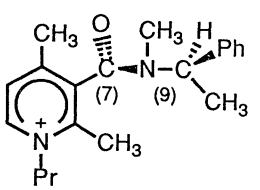
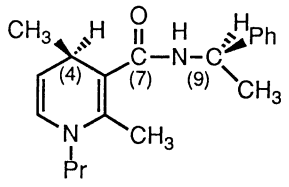
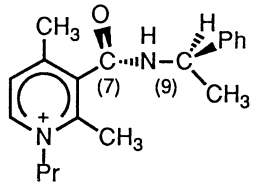


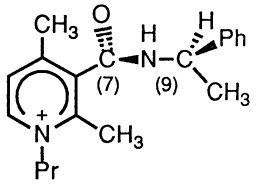
(7*S*,9*R*)-$Me_3PNP^+$



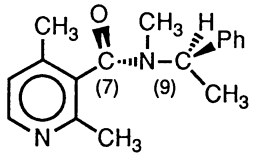
(4*R*,9*R*)-$Me_2$PNPH



(7*R*,9*R*)-$Me_2PNP^+$



(7*S*,9*R*)-$Me_2PNP^+$



(7*R*,9*R*)-$Me_3$PyP

## Results

**Absolute Configuration and Alkylation of 3-(*N*-methyl-*N*-α-methylbenzylcarbamoyl)-2,4-dimethylpyridine.** In order to study the chirality-transformation, it is neccessary to elucidate the absolute configuration at chiral centers. The absolute configuration with respect to the central chirality in $Me_3$PNPH has been established by the X-ray analysis on a similar compound, 3-(*N*-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethyl-1,4-dihydropyridine ($Me_2$PNPH).[5,6] The axial chirality in $Me_3PNP^+$, however, has not been studied yet. Since this onium salt is highly hygroscopic and did not afford a single crystal suitable for the X-ray crystallography, a crystal of 3-(*N*-methyl-*N*-(*R*)-α-methylbenzylcarbamoyl)-2,4-dimethylpyridine ((9*R*)-$Me_3$PyP) was employed for the structure analysis. Since it can be confirmed that a diastereoisomer which exerts the $C_2$-methyl signal at a lower field and $N_{carbamoyl}$-methyl signal at a higher field than the corresponding methyl signals from the other diastereoisomer in the $^1$H NMR spectrum of racemic $Me_3$PyP corresponds to the diastereoisomer of $Me_3PNP^+$ which exerts the $C_2$-methyl signal at a lower field and $N_{carbamoyl}$-methyl signal at a higher field, the absolute configuration of $Me_3PNP^+$ can be correlated directly to that of $Me_3$PyP.

The ORTEP drawing for the diastereoisomer which exerts the $C_2$-methyl signal at a lower field is shown in Fig. 1. Thus, the absolute configuration of this compound is (7*R*,9*R*). The plane of pyridine-ring and that of the carbonyl group in this isomer are set close to perpendicular each other, or the $C_2$–$C_3$–$C_7$–$O_{12}$ dihedral angle is −89.3°. In addition, the atoms $O_{12}$–$C_7$–$N_8$–$C_{13}$ are set in the same plane. That is, it is the $N_{carbamoyl}$-methyl group that produces the axial chiralities in $Me_3$PyP and its derivatives. Indeed, the axial chiralities in 3-(*N*-(*R*)-α-methylbenzylcarbamoyl)-

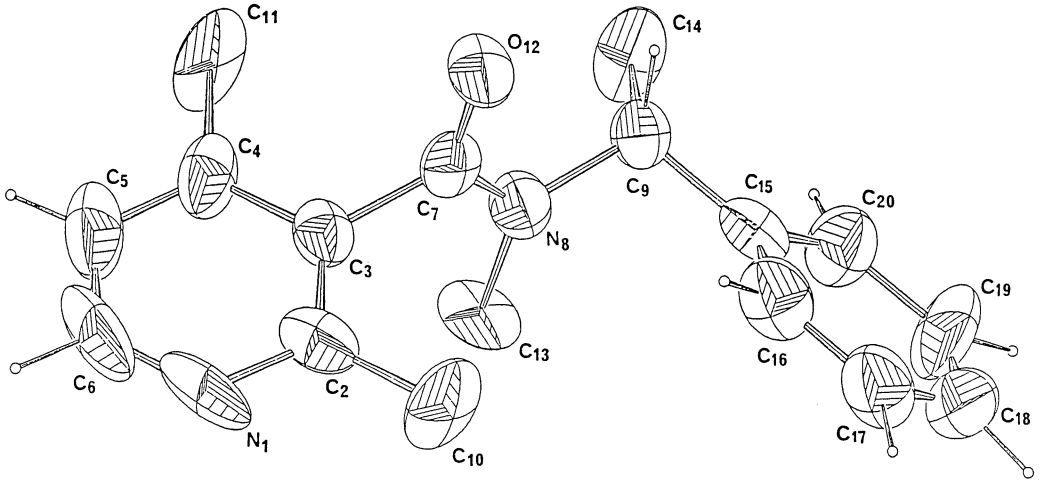



Fig. 1. ORTEP representation of (7*R*,9*R*)-$Me_2$PyP.

Table 1. Stereospecificity in the Oxidation in the Presence of Magnesium Ion

| 1,4-Benzoquinone | $E°$/V (vs. SCE)[a] | $R/S$ Ratio (Chemical yield/%) | | | |
|---|---|---|---|---|---|
| | | $Me_3$MQPH | $Me_3$MQPD | $Me_3$PNPH | $Me_3$PNPD |
| Unsubstituted | −0.50 | 1.0/4.9 (100) | 1.0/5.6 (100) | 1.0/3.9 ( 74) | — |
| Chloro- | −0.34 | 1.0/2.1 (100) | 1.0/2.1 ( 92) | 1.0/4.6 ( 90) | (49)[b] |
| 2,5-Dichloro- | −0.18 | 1.0/1.3 (100) | 1.0/1.4 ( 86) | 1.0/4.7 ( 79) | (57)[b] |
| 2,6-Dichloro- | −0.18 | 1.0/1.2 ( 77) | 1.0/1.2 ( 89) | 1.0/4.2 ( 90) | (53)[b] |
| Trichloro- | −0.13[c] | 1.2/1.0 (100) | 1.0/1.4 ( 71) | 1.0/4.1 ( 73) | (64)[b] |
| Tetrachloro- | −0.08 | 1.5/1.0 ( 94) | 1.0/1.3 ( 95) | 1.0/4.0 ( 68) | (88)[b] |
| 2,3-Dichloro-5,6-dicyano- | +0.51 | 1.1/1.0 ( 74) | 1.0/1.8 ( 62) | 1.0/4.2 (100) | (94)[b] |

a) Ref. 19. b) The $R/S$ ratio could not be determined. See Experimental for the detail. c) The mean of the values for 2,6-dichloro- and tetrachloro-1,4-benzoquinones.

Table 2. Stereospecificity in the Oxidation in the Absence of Magnesium Ion

| 1,4-Benzoquinone | $E°$/V (vs. SCE)[a] | $R/S$ Ratio (Chemical yield/%) | | | |
|---|---|---|---|---|---|
| | | $Me_3$MQPH | $Me_3$MQPD | $Me_3$PNPH | $Me_3$PNPD |
| Unsubstituted | −0.50 | b) | b) | b) | b) |
| Chloro- | −0.34 | 1.3/1.0 ( 7) | 1.0/1.0 ( 22) | 1.0/2.3 (36) | 1.0/2.9 (43) |
| 2,5-Dichloro- | −0.18 | 1.3/1.0 ( 9) | 1.2/1.0 ( 45) | 1.0/1.2 (47) | 1.0/1.0 (67) |
| 2,6-Dichloro- | −0.18 | 1.1/1.0 (36) | 1.2/1.0 ( 22) | 1.0/2.4 (51) | 1.0/2.3 (65) |
| Trichloro- | −0.13[c] | 2.0/1.0 (62) | 1.7/1.0 (100) | 1.0/1.5 (76) | 1.6/1.0 (76) |
| Tetrachloro- | −0.08 | 1.3/1.0 (85) | 1.2/1.0 ( 75) | 2.4/1.0 (68) | 2.4/1.0 (93) |
| 2,3-Dichloro-5,6-dicyano- | +0.51 | 1.0/1.0 (92) | 1.0/1.5 (100) | 1.0/1.2 (68) | (72)[d] |

a) Ref. 19. b) No reaction. c) The mean of the values for 2,6-dichloro- and tetrachloro-1,4-benzoquinones. d) The $R/S$ ratio could not be determined. See Experimental for the detail.

2,4-dimethylpyridine ($Me_2$PyP), the compound which has no methyl group on the carbamoyl-nitrogen, and its derivatives are too unstable to be fixed at room temperature, and their diastereoisomers are unable to be separated each other.

For the transformation of $Me_3$PyP into $Me_3PNP^+$ by the Menschutkin $N$-alkylation, it is neccessary, however, to run the reaction at low temperature in order to avoid undesirable racemization. Since the reaction of $Me_3$PyP with propyl bromide under an atmospheric pressure requires as high temperature as to reflux the solution, the alkylation was carried out at room temperature under a high pressure (10000 kg $cm^{-2}$) for 25 days, and $Me_3PNP^+$ thus obtained was recrystallized from chloroform. It was found that the propylation of (7*S*,9*R*)-$Me_3$PyP with propyl bromide yields a racemic mixture of (9*R*)-$Me_3PNP^+$, whereas (7*R*,9*R*)-$Me_3$PyP affords a 3:1 mixture of (7*R*,9*R*)- and (7*S*,9*R*)-$Me_3PNP^+$. On the other hand, methylation of (7*S*,9*R*)- and (7*R*,9*R*)-$Me_3$PyP with methyl iodide afforded the corresponding $N_{ring}$-methylated onium salt with 100% retention of the configuration.

**Stereochemistry of the Reaction.**[7] Oxidations of $Me_3$MQPH, $Me_3$MQPD, $Me_3$PNPH, and $Me_3$PNPD with various substituted and unsubstituted 1,4-benzoquinones in the presence or absence of magnesium ion in acetonitrile were run and the $R/S$ ratios with respect to the axial chirality in the corresponding onium salts were measured on $^1H$ NMR spectrometer. The results are summarized in Tables 1 and 2.

## Discussion

First of all, it is recognizable that the $R/S$ ratio in $Me_3MQP^+$ obtained from the reactions of $Me_3$MQPH without magnesium ion is not affected appreciably by the oxidation potentials of the quinones employed. However, in the presence of magnesium ion, the value of log ($R/S$) changes linearly from negative to positive as the oxidation potential of the quinone becomes larger. On the other hand, the $R/S$ ratio in $Me_3PNP^+$ obtained from the oxidations of $Me_3$PNPH in the absence of magnesium ion is affected by the oxidation potentials of the quinone, whereas the ratio stays at a constant value of 1/4—1/5 when magnesium ion exists in the reaction mixture.

In a previous paper where we reported the amine-catalyzed stereochemistry, we proposed that earliness and lateness of the transition state in the major process (with the highest activation energy, but not necessarily be the rate-determining step) of the reaction determine the syn/anti configurational preference[8] at the transition state: the early transition state prefers entropically favorable anti-conformation, but the late transition state prefers enthalpically favorable syn-conformation.[9] It was also proposed that the proton-transfer step is involved in the rate-determining step of the reaction of

$Me_3MQPH$, although the initial electron-transfer step requires larger activation energy than the proton-transfer step in the reaction with non-DDQ quinones.[9]

It is anticipated that the dihydroquinoline ring (a bicyclic system) will resist more strongly than the dihydropyridine ring (a monocyclic system) against the ring-deformation associated with their one-electron oxidation. Therefore, the former may require higher energy for oxidation (with less $C_4$–H bond deformation) than the latter. In other words, it is reasonable to expect that the transition-state in the stereo-determining step of the reaction with $Me_3MQPH$ comes earlier than that with $Me_3PNPH$.[10] Since the proton on the $C_4$-position is not dissociated enough in an early transition state, the reacting quinone has to come close to the substrate.

At the same time, $Me_3MQPH$ is sterically larger than $Me_3PNPH$. Both electronic and steric effects make the entropically favorable anti-configuration lower in Gibbs energy than enthalpically favored syn-configuration at the transition-state of the reaction with $Me_3MQPH$ as illustrated in Fig. 2.[9]

Magnesium ion is known to interact with both the electron-donor and -acceptor to make the two reacting components in closer approach as an ES-complex in an enzymatic reaction.[11,12] Since the oxidizing and reducing reagents face against each other by sandwiching a magnesium ion between them, steric tightness is less important here than in the reaction without magnesium ion, and the transition state in the reaction with magnesium ion feels no (or little) stress to assume enthalpically favored but entropically disfavored syn-configuration provided the reactivity of the quinone is low enough. The statement is equivalent to say that the presence of magnesium ion retards the abstraction of a proton to set the transition state late, because the coordination of the positively charged magnesium ion makes the radical anion of quinone less reactive toward the proton-abstraction.

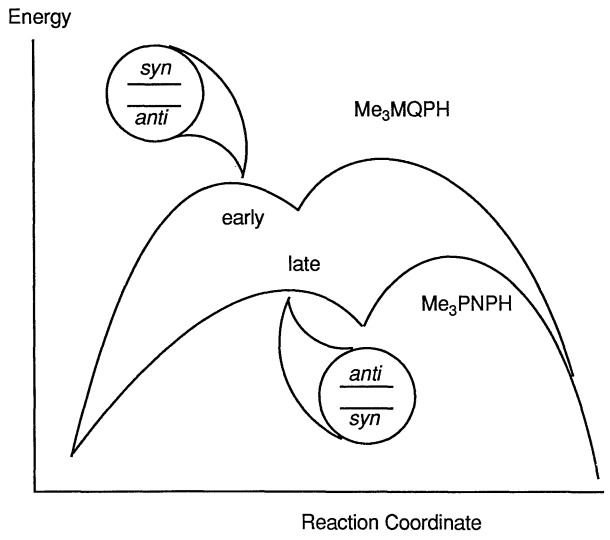



Fig. 2. Energy diagrams for the early and late transition states.

On the other hand, the transition state of the reaction with $Me_3PNPH$ is always later than that with $Me_3MQPH$ (with more $C_4$–H bond deformation) regardless the reactivity of the quinone,[9] and always passes through the syn-transition state even in the absence of magnesium ion. Of course, the presence of magnesium ion in this reaction shifts the specificity further toward the syn-preferency.

When the $C_4$-hydrogen in $Me_3MQPH$ is substituted by a deuterium, the energy barrier for the proton-transfer process becomes higher due to kinetic isotope effect, then the *R*/*S* ratio, or the stereospecificity of the reaction, may be the subject of the isotope effect.[13] It is seen in Table 1 that the stereospecificity is reversed by going from $Me_3MQPH$ (anti-preferency) to $Me_3MQPD$ (syn-preferency) in the reactions with the quinones of high reduction potentials such as DDQ, chloranil, and trichloro-1,4-benzoquinone in the presence of magnesium ion. The isotopic difference is not so significant in the absence of magnesium ion.

The results can also be interpreted in terms of tight and loose transition states: in the reaction with $Me_3MQPH(D)$, the proton-migrating step is affected by the isotopic substitution more sensitively than the initial electron-transfer step, and total energy barrier in the reaction of $Me_3MQPD$ becomes higher than that of $Me_3MQPH$. Thus, the formation of the electron-transfer intermediate is followed by the rate-determining second step in the reaction of the deuteriated compound. Under such a circumstance, the transition state for $Me_3MQPD$ is later and looser than that for $Me_3MQPH$ and the formation of (11*S*,13*R*)-$Me_3MQP^+$ is more preferred by the former than the latter. As the reactivity of the quinone decreases (or in the absence of magnesium ion as well), the energy barrier for the initial electron-transfer process becomes higher, and, consequently, relative importance of the difference in energy barrier for the proton-transfer process becomes less and the isotope effect becomes smaller.

## Experimental

**Instruments.** $^1H$ NMR spectra were recorded at 200 MHz and 400 MHz on a Varian VXR 200 FT-NMR and a JEOL JNM-GX400 FT-NMR spectrometers, respectively. $^2H$ NMR spectra were recorded at 31 MHz on a Varian VXR 200 FT-NMR spectrometer. UV spectra were obtained on a Hitachi U-3210 spectrophotometer with a Hitachi SDR-30 temperature controller. Elemental analyses were performed with a Yanaco MT-3 elemental analyzer.

**Materials.** Anhydrous solvents were prepared in the following way before the use: benzene, tetrahydrofuran (THF), and ether were distilled over sodium diphenyl ketyl. Acetonitrile was distilled over calcium hydride. Magnesium perchlorate was powdered, dried at 100 °C under reduced

pressure in the presence of diphosphorus pentaoxide, and placed in a sealed tube.

3-(*N*-(*R*)-α-methylbenzylcarbamoyl)-1,2,4-trimethylquinolinium iodide ($Me_2MQP^+I^-$),[14] (4*R*)-3-(*N*-(*R*)-α-methylbenzylcarbamoyl)-1,2,4-trimethyl-1,4-dihydroquinoline ($Me_2MQPH$)[14], 3-(*N*-(*R*)-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethylpyridinium bromide ($Me_2PNP^+Br^-$),[15] (4*R*)-3-(*N*-(*R*)-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethyl-1,4-dihydropyridine ($Me_2PNPH$),[15] and 3-(*N*-methyl-*N*-(*R*)-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethylpyridinium iodide ($Me_3PNP^+I^-$),[1] were prepared according to the literature procedures. Trichloro-1,4-benzoquinone was prepared according to the literature procedure.[16]

**Preparation of (4*R*)-3-(*N*-Methyl-*N*-(*R*)-α-methylbenzylcarbamoyl)-1,2,4-trimethyl-1,4-dihydroquinoline ($Me_3$-MQPH).** In a 20 ml round-bottomed flask equipped with a magnetic stirrer and sealed with a serum cap, 128 mg (0.40 mmol) of $Me_2MQPH$ and 227 mg (2.0 mmol) of potassium *t*-butoxide were placed. Then, the atmosphere inside the flask was replaced with nitrogen and 20 ml of anhydrous THF was injected into it through a syringe. The mixture was stirred for a while. The color turned pale yellow. Therein, 0.125 ml (2.0 mmol) of methyl iodide was injected dropwise with continuous stirring. An exothermic reaction occurred and white precipitates were formed. The mixture was stirred for an hour at room temperature in the dark under an atmosphere of nitrogen. The precipitates were filtered off and the filtrate was concentrated by evaporation of the solvent under reduced pressure. The residue was dissolved into dichloromethane. The solution was washed twice with water, dried over sodium sulfate, passed through a silica pad, and the solvent was evaporated under reduced pressure. $Me_3MQPH$ was obtained in 120 mg (0.35 mmol) as a slightly yellow oil in 87% yield. Spectral data were the same as those reported.[1] The 4-deuteriated compound was prepared similarly.

**Preparation of (4*R*)-3-(*N*-Methyl-*N*-(*R*)-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethyl-1,4-dihydropyridine ($Me_3$-PNPH).** $Me_2PNPH$ was methylated at the carbamoylnitrogen in 84% yield with the same procedure as described above. The 4-deuteriated compound was prepared similarly. It was recognized that all the six hydrogens in the $C_2$- and $C_4$-methyl groups exchanged with deuteriums during the 4-deuteration.

Although $Me_3PNPH$ is reasonably stable in a solution to be reacted with quinones and other oxidizing reagents, it decomposes immediately into unidentified product(s) when the solvent is evaporated completely under reduced pressure at room temperature or below, and elemental analysis of this compound does not give satisfactory results.

$^1H$ NMR ($CDCl_3$): $\delta^{TMS}$=0.89 (t, 3H), 1.11 (m, 3H), 1.53 (br.d, 3H), 1.84 (s, 3H), 2.73 (s, 3H), 2.8—3.3 (m, 3H), 4.45 (br.s, 1H), 6.18 (br.s, 1H), and 7.3—7.4 (m, 5H).

**Preparation of 3-(*N*-Methyl-*N*-(*R*)-α-methylbenzylcarbamoyl)-2,4-dimethylpyridine ((9*R*)-$Me_3PyP$).** In a 200 ml three-necked round-bottomed flask equipped with a magnetic stirrer and a reflux condenser protected with a calcium chloride tube, were placed 5 g (27 mmol) of 2,4-dimethylpyridine-3-carboxylic acid hydrochloride[15] and 28 ml (0.38 mol) of thionyl chloride. The solution was refluxed for 40 min. The color of the solution turned red. After excess thionyl chloride was removed by distillation under reduced pressure, the brown residue was obtained. Onto the residue, 13 ml of triethylamine dissolved in 20 ml of dichloromethane was added dropwise with stirring and cooling in an ice-salt bath. A brown solid precipitated. Subsequently, 3.7 g (30 mmol) of *N*-methyl-(*R*)-α-methylbenzylamine dissolved in 20 ml of dichloromethane was added to the solution over an hour with cooling in an ice-salt bath. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent keeping the temperature below 40 °C under reduced pressure, a brown residue was obtained. To the residue, 25 ml of concd hydrochloric acid and 100 ml of water were added and the solution was treated three times with activated charcoal. Thus obtained yellow solution was neutralized with sodium carbonate to obtain white precipitates. The reaction mixture was extracted with dichloromethane. The combined organic layer was washed with aqueous sodium hydrogencarbonate and two portions of water, and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a white solid, which was washed with ether to give 2.11 g (8.2 mmol) of $Me_3PyP$ in 30.4% yield. This is a mixture of two diastereomers with respect to the carbamoyl rotation.

Each diastereomers were partially separated by silica-gel column chromatography with a 1:1 mixture of acetone and hexane as an eluent. The crystals were recrystallized from a solution of chloroform in a refrigerator to obtain a single crystal of (7*R*,9*R*)-$Me_3PyP$; mp (uncorrected) 104—105 ° C for the (7*R*,9*R*)-isomer: 80—81 °C for the (7*S*,9*R*)-isomer.

Anal. Calcd for $C_{17}H_{20}N_2O$ (a 3/1 7*R*/7*S* mixture): C, 76.09; H, 7.51; N, 10.44%. Found: C, 75.98; H, 7.58; N, 10.35%.

$^1H$ NMR ($CDCl_3$): (7*R*,9*R*)-$Me_3PyP$ (earlier eluent); $\delta^{TMS}$= 1.64 (d, 3H), 2.31 (s, 3H), 2.44 (s, 3H), 2.47 (s, 3H), 6.32 (q, 1H), 7.02 (d, 1H), 7.30—7.48 (m, 5H), and 8.37 (d, 1H). (7*S*,9*R*)-$Me_3PyP$ (later eluent); $\delta^{TMS}$=1.64 (d, 3H), 2.25 (s, 3H), 2.43 (s, 3H), 2.52 (s, 3H), 6.32 (q, 1H), 6.98 (d, 2H), 7.30—7.48 (m, 5H), and 8.36 (d, 1H).

**Preparation of 3-(*N*-Methyl-*N*-(*R*)-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethyl-1,4-dihydropyridinium Bromide ($Me_3PNP^+Br^-$).** Into a Teflon tube, 106 mg (0.41 mmol) of $Me_3PyP$ and 3.4 g (27 mmol) of propyl bromide in 2 ml of ethanol were placed. The tube was placed in an autoclave under high pressure (10000 kg cm$^{-2}$) for 25 days at room temperature to undergo the reactions. After the evaporation of the ethanol under reduced pressure, the residue obtained in quantitative yield was washed with ether and subjected to $^1H$ NMR spectroscopy. The $Me_3PNP^+Br^-$ obtained from (7*R*,9*R*)-$Me_3PyP$ was diastereomerically purer than that obtained from (7*S*,9*R*)-$Me_3PyP$, which was an equivalent mixture of the two diastereoisomers. This compound is too hygroscopic to obtain satisfactory results from elemental analysis.

$^1H$ NMR ($CDCl_3$): $Me_3PNP^+Br^-$ from (7*R*,9*R*)-$Me_3PyP$; $\delta^{TMS}$=1.00 (m, 3H), 1.15 (d, 3H), 1.85 (m, 2H), 2.52 (s, 3H), 2.53 (s, 3H), 2.61 (s, 3H), 4.56 (q, 2H), 6.08 (q, 1H), 7.3—7.5 (m, 5H), 7.88 (d, 1H), and 8.98 (d, 1H). $Me_3PNP^+Br^-$ from (7*S*,9*R*)-$Me_3PyP$; in addition to the signals listed above $\delta^{TMS}$=2.40 (s, 3H), 2.51 (s, 3H), and 2.71 (s, 3H).

**X-Ray Analysis.** Crystal data of $Me_3PyP$ are as follows: MW=268.36. Orthorhombic. Space group $P2_12_12_1$. $a$= 14.471(1), $b$=14.483(2), $c$=7.387(1) Å. $V$=1548.2(0.7) Å$^3$, $Z$=4 molecules/cell, and $D_c$=1.156 g cm$^{-3}$.

A piece of crystal (size 0.4×0.4×0.5 mm$^3$) was used for the

data collection. Cell dimensions were determined by least squares calculations with $2\theta$ values of 25 reflections measured on a Rigaku AFC-5FOS four-circle diffractometer by using graphite-monochromated Mo-$K\alpha$ radiation ($\lambda$= 0.7107 Å). Intensity data of 1537 reflections with $2\theta \leq 55°$ were collected by the use of the $\theta$-$2\theta$ mode with a scanning rate of 16° $min^{-1}$ in $2\theta$. The reflection data were not corrected for absorption.

All of the reflections were used for solution. The structure was solved by means of MULTAN 84.[17] Block-diagonal least squares refinement with anisotropic temperature factors for non-hydrogen atoms converged successfully to $R$=0.067. Eight hydrogen atoms were included in computation. Calculations were performed on FACOM S3500 superminicomputer in TASMAC, ISIR, Osaka University.

Selected torsional angles are as follows: $\angle C_4$-$C_3$-$C_7$-$O_{12}$= 82.5°, $\angle C_4$-$C_3$-$C_7$-$N_8$=−95.9°, $\angle C_2$-$C_3$-$C_7$-$O_{12}$=−89.3°, $\angle C_2$-$C_3$-$C_7$-$N_8$=92.3°, $\angle C_{11}$-$C_4$-$C_3$-$C_7$=9.0°, $\angle O_{12}$-$C_7$-$N_8$-$C_9$=0.3°, $\angle O_{12}$-$C_7$-$N_8$-$C_{13}$=−177.8°.

The complete $F_o$−$F_c$ data are deposited as Document No. 9092 at the Office of the Editor of Bull. Chem. Soc. Jpn.

**Reaction.** In a 50 ml round-bottomed flask equipped with a magnetic stirrer and sealed with a serum cap, 0.03 mmol of a 1,4-benzoquinone derivative was placed. Then, the atmosphere inside the flask was replaced with argon and 28 ml of anhydrous acetonitrile was injected through a syringe. To the solution, 2 ml of acetonitrile solution containing 10 mg (0.03 mmol) of $Me_3MQPH$ (and 6.7 mg (0.03 mmol) of magnesium perchlorate, if necessary) was injected through a syringe. Then, the mixture was stirred for 24 h at room temperature in the dark. After evaporation of the solvent below 40 °C under reduced pressure, the residue was washed twice with ether and the crude $Me_3MQP^+$ was dissolved in $CD_3CN$ and subjected to $^1H$ NMR spectroscopy to elucidate the diastereomer ratio and the yield of the product. The $^1H$ NMR spectrum of $Me_3MQP^+$ thus obtained was the same as that reported.[1] The $R/S$ ratio was measured by means of the $N_{ring}$-methyl signals (for $Me_3MQP^+$) or the $C_2$- and $C_4$-methyl signals (For $Me_3PNP^+$). Therefore, in principle, the ratio in $Me_3PNP^+$ produced from $Me_3PNPD$ (i.e. $(CD_3)_2MePNP^+$) could not be measured. However, the deuteriums in $(CD_3)_2MePNP^+$ again exchanged with hydrogens during the reaction without magnesium ion, probably due to the presence of trace amount of water in the solvent. Magnesium perchlorate is a well-known drying agent.[18] No doubt that the hydrogen-deuterium exchange does not affect the stereochemistry.[13]

It was confirmed, using 1:1 and 3:1 mixtures of the diastereoisomers, that the conformation of $Me_3MQP^+$ is sufficiently stable during the reaction, work-up and the spectroscopy.

The stereospecificities in the reactions with other compounds were determined similarly.

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7) In the present research, the compounds we employed always have the $R$-configuration at the $\alpha$-methylbenzyl group on the amide-nitrogen. At the same time, the configuration at the $C_4$-position in $Me_3MQPH(D)$ or $Me_3PNPH(D)$ is always $R$. Therefore, we will neglect hereafter, for simplicity of the discussion, the signs to indicate the chirality at these positions in these compounds, unless neccessary. With this understanding, we can only deal with the axial chiralities in $Me_3MQP^+$ or $Me_3PNP^+$, which will be indicated by $R$ or $S$ without specifying the position. Stereospecificity of the reaction has been confirmed using other diastereoisomers of $Me_3MQPH$ and $Me_3PNPH$.[2]

8) The *anti*-transition state is the one in which the $C_4$–H and C=O bonds in $Me_3MQPH$ or $Me_3PNPH$ point the opposite face of the molecular plane each other, whereas these bonds point the same face in the *syn*-transition state.

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