NAD(P$^+$)/NAD(P)H Models. 83. Molecular Asymmetry with a Carbonyl Group: Electronically Controlled Stereochemistry in the Reaction of NAD(P)$^+$/NAD(P)H Analogs

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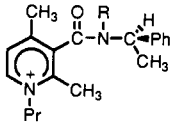
Abstract: The *N*-methylpyridinium salt of 6,7-dihydro-6-methyl-5-oxopyridino[3,2-*d*]-2-benzazepin has been synthesized. The salt has axial chirality with respect to the orientation of the carbonyl dipole. An enantiomer of the cation has been obtained as the iodide salt. Reduction of the salt results in the corresponding dihydropyridine derivative stereospecifically. The stereochemistry of the reduction is controlled entirely by the electronic effect of the carbonyl dipole.

Introduction

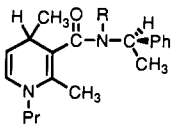
Although pyridinium/dihydropyridine moieties in NAD(P)$^+$/NAD(P)H coenzymes are achiral, *re*- and *si*-faces of the molecules are recognized by a substrate when they are set in a pocket of an enzyme. Some oxidoreductases prefer the *re*-face, while others react on the *si*-face. From the viewpoint of chemical evolution of an enzyme, the difference in stereochemistry as well as the mechanism involved is an interesting subject. There are two possibilities for the stereochemical evolution of oxidoreductases to the present forms: functional and random.[1]

Nambiar and co-workers have proposed a hypothesis that the stereochemistry of dehydrogenases depends on the reactivity of the (native) substrate.[2] Although this hypothesis has been criticized[3,4] and there are exceptions,[5] the hypothesis still serves as a focus for experimental tests. Namely, the exceptions are not exceptions when the relative importance of the direction of reactions (oxidation or reduction) is taken into account for these particular enzymes in nature.[5,6]

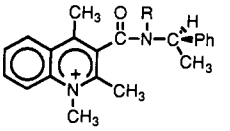
In previous papers, we reported homogeneous reaction systems where the stereochemistry of chiral NAD(P)$^+$/NAD(P)H analogs (Me_3PNP^+/Me_3PNPH and Me_3MQP^+/Me_3MQPH), in which the stereochemical course of the redox reaction is influenced by the orientation of a carbonyl group, is controlled by the reactivity of a substrate,[7-11] in contrast to the conclusion presented by Brounts and Buck based on quantum mechanical calculations.[12] As these authors have mentioned, the substrate assigned for the calculation carries a positive charge, and the charge–dipole interaction appears to be important in these calculations when the carbonyl dipole is syn to the reacting hydrogen. Since the stereochemistry observed in these organic systems is exactly parallel[7] to those of enzymatic systems classified by Nambiar *et al.*,[2] we studied the mechanism for stereochemical control in this and similar systems extensively and came to a conclusion that the interaction at the ground state is quite important.[13-15]



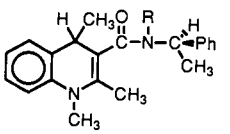
R=H : Me_2PNP^+
R=CH_3 : Me_3PNP^+



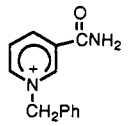
R=H : Me_2PNPH
R=CH_3 : Me_3PNPH



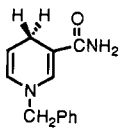
R=H : Me_2MQP^+
R=CH_3 : Me_3MQP^+



R=H : Me_2MQPH
R=CH_3 : Me_3MQPH



BNA^+



BNAH

Experimental Section

Instruments. Melting points were obtained on a Yanagimoto micro-melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at 200 and 400 MHz on Varian VXR 200 FT-NMR and JEOL

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(1) Benner, S.; Stackhouse, J. In *Chemical Approaches to Understanding* Enzyme Catalysis; Green, B. S., Ashani, Y., Chipman, D., Eds.; Elsevier: New York, 1982.
(2) Nambiar, K. P.; Stauffer, D. M.; Koloziej, P. A.; Benner, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 5886-5890.
(3) Oppenheimer, N. J. *J. Am. Chem. Soc.* **1984**, *106*, 3032-3033.
(4) Schneider-Bernlöhr, H.; Adolph, H.-W.; Zeppezauer, M. *J. Am. Chem. Soc.* **1986**, *108*, 5573-5576.
(5) Benner, S. A.; Nambiar, K. P.; Chambers, G. K. *J. Am. Chem. Soc.* **1985**, *107*, 5513-5517.
(6) Nakamura, K.; Shiraga, T.; Miyai, T.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1735-1737.
(7) Ohno, A.; Ohara, M.; Oka, S. *J. Am. Chem. Soc.* **1986**, *108*, 6438-6440.
(8) Ohno, A.; Ogawa, M.; Oka, S. *Tetrahedron Lett.* **1988**, *29*, 3079-3082.
(9) Ohno, A.; Kashiwagi, M.; Ishihara, Y. *Tetrahedron* **1986**, *42*, 961-973.
(10) Ohno, A.; Ogawa, M.; Oka, S. *Tetrahedron Lett.* **1988**, *29*, 1951-1954.
(11) Okamura, M.; Kashiwagi, T.; Mikata, Y.; Maruyama, T.; Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 1475-1478.
(12) Brounts, R. H. A. M.; Buck, H. M. *J. Am. Chem. Soc.* **1983**, *105*, 1284-1288.
(13) Ohno, A.; Goto, M.; Mikata, Y.; Kashiwagi, T.; Maruyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 87-90.
(14) Okamura, M.; Mikata, Y.; Yamazaki, N.; Tsutsumi, A.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1191-1196.
(15) Okamura, M.; Mikata, Y.; Yamazaki, N.; Tsutsumi, A.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1197-1203.

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JNM-GX 400 FT-NMR spectrometers, respectivity. Infrared spectra were collected on a JASCO FT/IR-5300 spectrometer. Elemental analyses were performed with a Yanaco MT-3 Elemental Analyzer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Circular dichroism spectra were collected on a JASCO J-720 spectropolarimeter.

Materials. 2–Chloronicotinic acid and 2-bromobenzyl bromide were purchased from Tokyo Kasei Co. Ltd. (1*S*)-(+)-Camphorsulfonic acid was purchased from Nacalai Tesque Co. Ltd. $NiBr_2(PPh_3)_2$ was prepared according to the literature procedure.[16] THF was freshly distilled in the presence of sodium benzophenone ketyl immediately prior to the use. Other chemicals were of reagent grade and were used without purification. Column chromatography was performed with silica gel 60 (Nacalai Tesque, 70-230 mesh).

Standard workup means that the organic layers were washed with brine and water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pessure.

Preparation of 3-(*N*-Methyl-*N*-(2′-bromobenzyl)carbamoyl)-2-chloropyridine (2a). 3-(*N*-Methyl-*N*-(2′-bromobenzyl)carbamoyl)-2-chloropyridine (**2a**) was prepared by a method similar to one reported previously.[17] Into a 200-mL, round-bottomed, three-necked flask equipped with a magnetic stirring bar and a reflux condenser protected by an alkaline trap were placed 2-chloronicotinic acid (4.2 g, 27 mmol) and thionyl chloride (32 mL, 0.4 mol), and the solution was refluxed for 1 h. The solution turned brown. After excess thionyl chloride was removed by distillation under reduced pressure, a brown residue was obtained. Triethylamine (20 mL) dissolved in CH_2Cl_2 (35 mL) was poured to the residue in an ice bath with stirring and cooling. Subsequently, (2-bromobenzyl)methylamine (6 g, 30 mmol) dissolved in CH_2Cl_2 (35 mL) was added to the solution over 30 min with cooling in an ice bath. After the reaction mixture was stirred for 2 h at room temperature, H_2O (100 mL) was added, followed by standard workup. The residue was purified by column chromatography with ethyl acetate as an eluent. Subsequent recrystallization of the eluted material from ethanol afforded 5.36 g of **2a** as colorless crystals: yield 47%; mp 89.5–90.0 °C; IR (KBr): 1649, 1392, 1298, 1101, 1026, and 758 cm^{-1}. ^1H NMR ($CDCl_3$), E/Z = 2/1. *E*: δ 2.02 (s, 3H, 6-CH_3), 4.93 (bd, 2H, CH_2), 7.16–7.62 (m, 5H, arom), 7.73 (dd, J = 2.0 Hz, 1H, arom), 8.47 (dd, J = 2.0 Hz, 1H, arom). *Z*: δ 3.10 (s, 3H, 6-CH_3), 4.46 (s, 2H, CH_2), 7.16–7.62 (m, 6H, arom), 8.42 (dd, J = 2.0 Hz, 1H, arom). Anal. Calcd for $C_{14}H_{12}N_2BrClO$: C, 49.51; H, 3.55; N, 8.24. Found: C, 49.51; H, 3.49; N, 8.24.

Preparation of 6,7-Dihydro-6-methyl-5-oxopyridino[3,2-*d*]-2-benzazepin (3a). Into a 300-mL, round-bottomed, two-necked flask containing a magnetic stirring bar were placed $NiBr_2(PPh_3)_2$ (2.23 g, 3 mmol), zinc (981 mg, 15 mmol), and Et_4NI (1.66 g, 6.47 mmol). The flask was degassed and filled with argon several times. Dry THF (60 mL) was added through a syringe, and the mixture was stirred at room temperature. After the reddish brown catalyst had formed (30 min), an argon-purged solution of **2a** (2.2 g, 6.47 mmol) in the same solvent (150 mL) was added through a syringe. The reaction mixture was stirred for 2 h at room temperature under an argon atmosphere.[18] After the inorganic precipitate was removed by filtration and washed with CH_2Cl_2, the filtrate and washings were combined, and the solvent was evaporated under reduced pressure. The residue was extracted with 1 M hydrochloric acid (100 mL × 2) and neutralized with aqueous sodium hydroxide to precipitate white solid. The residue was removed by filtration, and the product was extracted from the filtrate with ethyl acetate. Recrystallization of the extracted material from diethyl ether afforded 0.4 g of **3a** as white crystals: yield 42%; mp 132.0–132.5 °C. IR (KBr): 1645, 1421, 773, and 748 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.21 (s, 3H, 6-CH_3), 3.94 (bd, J = 12.8 Hz, 1H, CH_2), 4.51 (bd, J = 12.8 Hz, 1H, CH_2), 7.28–7.56 (m, 4H, arom), 8.07 (dd, 1H, arom), 8.31 (dd, 1H, arom), 8.81 (dd, 1H, arom). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.72, H, 5.37; N, 12.50.

Preparation of 6,7-Dihydro-6-methyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepinium Iodide (1a). Into a 50-mL, round-bottomed flask equipped with a reflux condenser protected with a tube of calcium chloride were placed **3a** (0.5 g, 2.23 mmol) and methyl iodide (4 g, 22.3 mmol) in DMF (15 mL). The reaction mixture was stirred for 7 h at 75 °C, and the solution turned a yellow. After DMF was removed by distillation under reduced pressure, a yellow residue was obtained. The residue was washed with hexane several times and dried under reduced pressure. Recrystallization of the residue from methanol afforded 0.49 g of **1a** as yellow crystals: yield 60%, mp 206–207 °C. IR (KBr): 3535, 1633, 1483, 1433, and 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.15 (s, 3H, 6-CH_3), 4.00 (d, J = 15.2 Hz, 1H, CH_2), 4.57 (s, 3H, 1-CH_3), 5.31 (d, J = 15.2 Hz, 1H, CH_2), 7.52–7.72 (m, 4H, arom), 8.14 (dd, J = 8.2, 6.2 Hz, 1H, arom), 8.82 (dd, J = 8.2, 1.2 Hz, 1H, arom), 9.50 (dd, J = 6.2, 1.2 Hz, 1H, arom). Anal. Calcd for $C_{15}H_{15}N_2IO$: C, 49.22; H, 4.13; N, 7.65. Found: C, 49.12; H, 4.09; N, 7.64.

Preparation of 6,7-Dihydro-6-*tert*-butyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepinium Iodide (1b). 6,7-Dihydro-6-*tert*-butyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepinium iodide (**1b**) was prepared by the same method as described above for preparation of **1a**.

2b: colorless crystals; 76% yield; mp 148.0–149.0 °C. IR (KBr): 2974, 1645, 1394, 1197, and 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.57 (s, 9H, *t*-Bu), 4.25 (bd, J = 17.6 Hz, 1H, CH_2), 4.73 (bd, J = 17.6 Hz, 1H, CH_2), 7.02–7.16 (m, 2H, arom), 7.32–7.47 (m, 4H, arom), 8.31 (dd, 1H, arom). Anal. Calcd for $C_{17}H_{18}N_2BrClO$: C, 53.49; H, 4.75; N, 7.33. Found: C, 53.59; H, 4.75; N, 7.30.

3b: colorless crystals; 31% yield; mp 106.0–107.0 °C. IR (KBr): 1631, 1396, 1195, and 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.55 (s, 9H, *t*-Bu), 4.13 (d, J = 15.6 Hz, 1H, CH_2), 4.52 (d, J = 15.6 Hz, 1H, CH_2), 7.32–7.55 (m, 4H, arom), 8.14 (dd, 1H, arom), 8.31 (dd, 1H, arom), 8.78 (dd, 1H, arom). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.76; H, 6.82; N, 10.53. Found: C, 76.53; H, 6.84; N, 10.42.

1b: yellow crystals; 77% yield; mp 240 °C dec. IR (KBr): 2974, 1637, 1398, 1192, 1105, and 758 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-Bu), 4.54 (s, 3H, 1-CH_3), 4.60 (d, J = 16.0 Hz, 1H, CH_2), 4.84 (d, J = 16.0 Hz, 1H, CH_2), 7.53–7.74 (m, 4H, arom), 8.09 (dd, 1H, arom), 8.75 (dd, 1H, arom), 9.48 (dd, 1H, arom). Anal. Calcd for $C_{18}H_{21}N_2IO$: C, 52.95; H, 5.18; N, 6.86. Found: C, 53.01; H, 5.23; N, 6.87.

Preparation of Diastereomerically Pure Salt of 1a. Silver (1*S*)-(+)-10-camphorsulfonate was prepared quantitatively by mixing equivalent amounts of (1*S*)-(+)-10-camphorsulfonic acid and silver oxide in CH_3CN in the dark. Into a 50-mL, round-bottomed flask were placed **1a** (0.11 g, 0.3 mmol) and silver (1*S*)-(+)-10-camphorsulfonate (0.1 g, 0.3 mmol) in CH_3CN (10 mL). The reaction mixture was stirred for 30 min at room temperature in the dark. After separation of inorganic precipitate by filtration, CH_3CN was removed from the filtrate by evaporation to give **1a** quantitatively as white residue. The salt was recrystallized from hexane/CH_2Cl_2 (1/1, v/v) at room temperature to afford 79 mg of the diastereomerically pure salt of **1a** as colorless crystals: yield 46%; mp 174–176 °C.

The anion of the thus obtained (+)-10-camphorsulfonate salt of **1a** was exchanged to the iodide by subjecting the salt to column chromatography packed with the iodide form of IRA-400 anion-exchange resin at 5 °C, and the eluted aqueous solution was freeze-dried immediately. The iodide salt remaining as residue exerted optical activity of $[\alpha]^{15}_D$ +268° (H_2O, c = 0.629).

Kinetics for Racemization. The kinetics for racemization of the diastereomeric salt in aqueous solutions was followed polarimetrically at 15.0, 25.0, 35.0, and 47.3 °C in H_2O (c = 0.151). The kinetics at 25 °C in $CHCl_3$ (c = 0.525) and CH_3CN (c = 0.51) were also measured polarimetrically. In addition, racemization of the (+)-10-camphorsulfonate salt of **1a** in $CDCl_3$ at 25 °C was followed by the ^1H NMR spectroscopic method by observing the ratio of intensities of signals from the diastereotopic methylene protons in the azepin ring. Rate constants for racemization were calculated by the least-squares curve-fit using a personal computer.

Reduction. Into a 10-mL, round-bottomed flask was placed **1a** (30 mg, 0.082 mmol) dissolved in degassed 0.5 M Na_2CO_3/D_2O solution (0.5 mL). After CH_2Cl_2 (1.0 mL) was added through a syringe with stirring, sodium hydrosulfite (0.14 g, 0.82 mmol) dissolved in degassed 0.5 M Na_2CO_3/D_2O solution (0.5 mL) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. The organic and water layers were separated, the former was dried, and the solvent was evaporated under reduced pressure. The crude residue was dissolved in CD_3CN and subjected to 400-MHz ^1H NMR spectroscopy to elucidate the stereochemistry (the orientation of the C_4—D bond with respect to the C=O bond) of the (net) deuteride-transfer reaction between **1a** and a deuterated reducing reagent.

The reaction with **1b** was carried out similarly except for the use of a phosphate buffer solution of pH 7.5 in place of D_2O.

Alternatively, in an NMR tube were **1a** or **1b** (0.014 mmol) and BNAH-4,4-d_2 or 4*R*(or 4S)-Me_2PNPH-4-*d* (0.042 mmol) in CD_3CN (700 μL).

(16) Venanzi, L. M. *J. Chem. Soc.* **1958**, 719.

(17) Ohno, A.; Mikata, Y.; Goto, M.; Kashiwagi, T.; Tanaka, T.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 81.

(18) Iyoda, M.; Otsuka, H.; Sato, K.; Oda, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80.

Table 1. Crystallographic Parameters of the Diastereomerically Pure Salt of **1a**

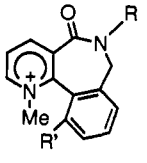
formula	$C_{25}H_{32}N_2SO_6$
FW	488.60
cryst color, habit	colorless, prismatic
cryst dimens, mm	0.40 × 0.30 × 0.24
cryst system	monoclinic
space group	$P2_1$ (No. 4)
lattice type	primitive
lattice params	a = 9.049(3) Å
	b = 9.668(2) Å
	c = 14.022(2) Å
	β = 98.98(2)°
	V = 1211.7(5) Å^3
Z	8
D_{calc}, g cm^{-3}	1.339
radiation	Cu Kα (λ = 1.541 78 Å)
μ, cm^{-1}	15.54
$2\theta_{max}$, deg	120.0
refinement	full-matrix least-squares
no. of measd reflcns	2059
no. of indep reflcns ($I > 3.00\sigma(I)$)	1806
R	0.033
R_w	0.034

The reaction was carried out for 39 h at 35 °C (with BNAH) or for 1.5 h at 25 °C (with Me_2PNPH) under an argon atmosphere.

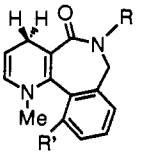
Crystallographic Studies. A colorless prismatic crystal of diastereomerically pure (+)-10-camphorsulfonate salt with dimensions 0.40 × 0.30 × 0.24 mm^3 was used for data collection. The lattice parameters and intensity data were measured on a Rigaku AFC7R diffractometer and a 18-kW rotating anode generator with 8-kW Cu Kα radiation. The structure was solved by direct methods, and the non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1806 observed reflections to give R = 0.033 and R_w = 0.034. All calculations were performed using a TEXSAN crystallographic software package developed by Molecular Structure Corp. (1985 and 1992). An ORTEP drawing is presented in Figure 2, and crystallographic parameters are listed in Table 1.

Results and Discussion

Since Me_nPNP$^+$/Me_nPNPH and Me_nMQP$^+$/Me_nMQPH have methyl groups at their 4-positions, the 4-positions in Me_nPNPH and Me_nMQPH are stereogenic, which is not true for NAD(P)H. In order to obtain a closer analog of NAD(P)$^+$/NAD(P)H coenzymes for testing the orientational effect of the carbonyl group more directly, we synthesized an *N*-methylpyridinium salt of 6,7-dihydro-6-methyl-5-oxopyridino[3,2-*d*]-2-benzazepin (MeMPA$^+$) and its dihydropyridine derivative (MeMPAH).



R=Me, R'=H : MeMPA$^+$
R=^{t}Bu, R'=H : BuMPA$^+$
R=Me, R'=Me : 3Me-MeMPA$^+$



R=Me, R'=H : MeMPAH
R=^{t}Bu, R'=H : BuMPAH
R=Me, R'=Me : 3Me-MeMPAH

Since Me_nPNP$^+$ and Me_nMQP$^+$ have not only axial chiralities but also a stereogenic center, the α-methylbenzyl group in their side chains, the faces of these molecules are *diastereotopic*. The faces of MeMPA$^+$, on the other hand, are *enantiotopic*, and the cation racemizes only through conformational changes that change the orientation of the carbonyl group.[19]

Unfortunately, conformational stability of MeMPA$^+$I$^-$ is not sufficient, and the optically active enantiomer of this salt racemizes at room temperature easily. A racemic mixture of MeMPA$^+$I$^-$ was synthesized according to a practical procedure shown in Scheme 1, and the mixture was subjected to preparative HPLC on CHIRALCEL AS at 5 °C to afford each enantiomeric conformer.[19] The racemic salt was also subjected to resolution by changing the counteranion from iodide to (+)-camphorsulfonate. An enantiomer of the (+)-camphorsulfonate salt thus obtained was subjected to anion-exchange resin (iodide form of IRA-400) at 5 °C, and the eluted aqueous solution was freeze-dried. The iodide salt remaining as residue exhibited optical activity of $[\alpha]^{15}_D$ +268° (water, c = 0.629). The CD spectrum of the salt is shown in Figure 1. The possibility of contamination by (+)-camphorsulfonate in the (+)-MeMPA$^+$I$^-$ salt thus obtained was excluded by an analysis of the CD and UV/vis absorption spectra: upon the salt standing at 45 °C for overnight, enantiomeric conformations equilibrated, and no optical rotation due to contamination of (+)-camphorsulfonate was detected ($[\alpha]^{15}_D$ 0.00° (water, c = 0.629)).

The (+)-camphorsulfonate salt was subjected to X-ray crystallographic analysis, and its ORTEP structure is illustrated in Figure 2. Thus, we confirmed that the absolute configuration of (+)-MeMPA$^+$ is *R*, where the pyridinium moiety assumes an almost flat conformation and the carbonyl group extends from

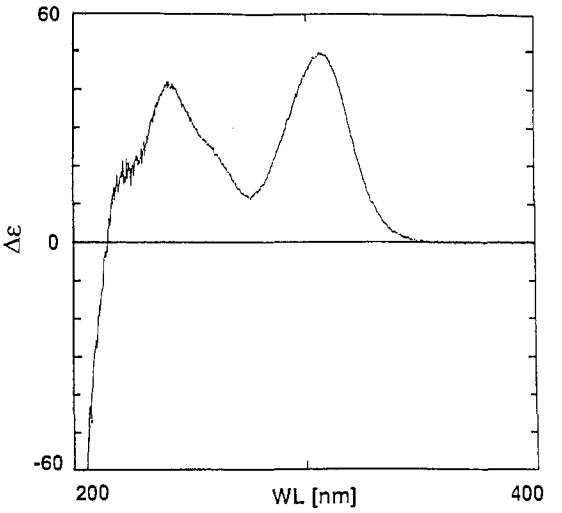


Figure 1. Circular dichroism (CD) spectrum of (+)-(*R*)-6,7-dihydro-6-methyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepinium iodide (MeMPA$^+$I$^-$).

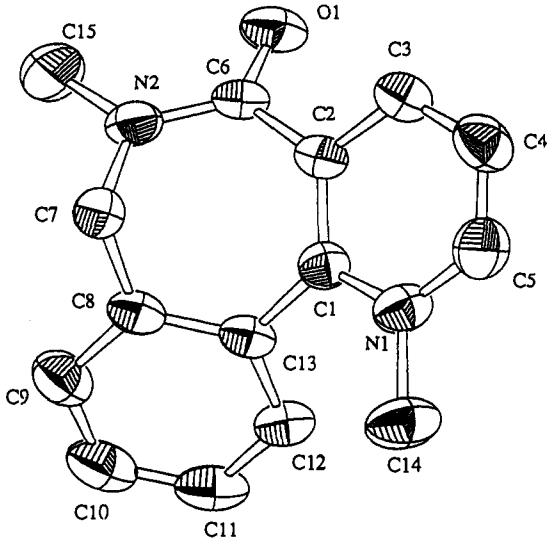
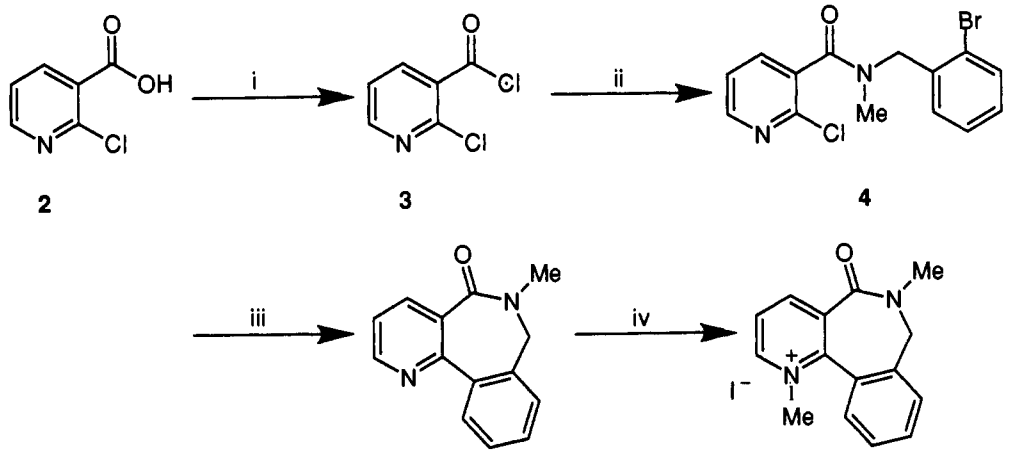


Figure 2. ORTEP drawing of (+)-(*R*)-6,7-dihydro-6-methyl-5-oxo*N*-methylpyridino[3,2-*d*]-2-benzazepinium (+)-camphorsulfonate (MeMPA$^+$C$_{10}$H$_{15}$O$_4$S$^-$). The anion part is omitted from the figure for simplicity.

(19) Orientation of the phenyl moiety constitutes another axial chirality. However, since the orientation of phenyl group is always subordinate to the orientation of carbonyl group when they occupy the same face, as can be seen in Figure 2, attention on this axial chirality is neglected for simplicity of the discussion.

Scheme I[a]



[a] Reagents and conditions: (i) $SOCl_2$, reflux, 1 h; (ii) Et_3N, (2-bromobenzyl)methylamine, methylenechloride (CH_2Cl_2), room temperature, 2 h, 47%; (iii) Zn, $NiBr_2(PPh_3)_2$, Et_4NI, tetrahydrofuran (THF), room temperature, Ar, 2 h, 42%; (iv) excess MeI, dimethylformamide (DMF), 75 °C, 7 h, 60%.

Table 2. Unimolecular Rate Constants for Racemization of (+)-(*R*)-*N*-Methylpyridinium Salt from 6,7-Dihydro-6-methyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepin ($MeMPA^+X^-$)[a] in Various Solvents

solvent	temp, °C	X[a]	$10^4 k_{rac}$[b]/s^{-1}	$t_{1/2}$/min
$CHCl_3$	25.0	CS	6.50 ± 0.01	17.8
CH_3CN	25.0	CS	8.52 ± 0.02	13.6
H_2O	15.0	I	0.56 ± 0.001	206
H_2O	25.0	CS	2.28 ± 0.02	50.7
H_2O	35.0	CS	4.78 ± 0.10	24.7
H_2O	47.3	CS	16.92 ± 0.05	6.83

[a] CS, (+)-camphorsulfonate. [b] $k_{rac} = 2k_{inversion}$.

the plane at an angle of 40°, conferring an axial chirality. The phenyl group occupies the same face as the carbonyl oxygen, and the dihedral angle in the CH_3—N—C=O moiety in the seven-membered ring is only 5.4°, indicating strong double-bond character between the amide nitrogen and carbonyl carbon. Thus, this cation has a very tight conformation.

6,7-Dihydro-6-*tert*-butyl-5-oxopyridino[3,2-*d*]-2-benzazepin ($BuMPA^+$) was synthesized similarly. Although enantiomers of this salt are separable on a CHIRALCEL OD at room temperature, isolation of each enantiomer has not yet been achieved. The (+)-camphorsulfonate salt of this cation does not exhibit separated signals for diastereomeric hydrogens in ^1H NMR, and no single crystal suitable for X-ray crystallography has been obtained.

Kinetics for racemization of $MeMPA^+$ in various solvents have revealed that water stabilizes the conformation, probably due to the contribution of hydrogen bonding. Results are listed in Table 2.

Analysis of temperature-dependent kinetics for racemization of (+)-$MeMPA^+$, which was followed polarimetrically in a temperature range of 15.0–47.3 °C, reveals that the energy of activation, E_a, for racemization of (+)-$MeMPA^+$ in water is 18.8 kcal·mol^{-1}. This value is comparable to that for ring inversion of dibenz[*c*,*e*]azepin (E_a = 20.6 kcal·mol^{-1}) reported recently.[20] An excellent linear relationship observed in an inclusive Arrhenius plot of the iodide and (+)-camphorsulfonate salts, as shown in Figure 3, suggests that the rate of racemization is not affected by the counteranion.

The ^1H NMR spectrum of MeMPAH in CD_3CN shows completely separated signals arising from two methylene protons

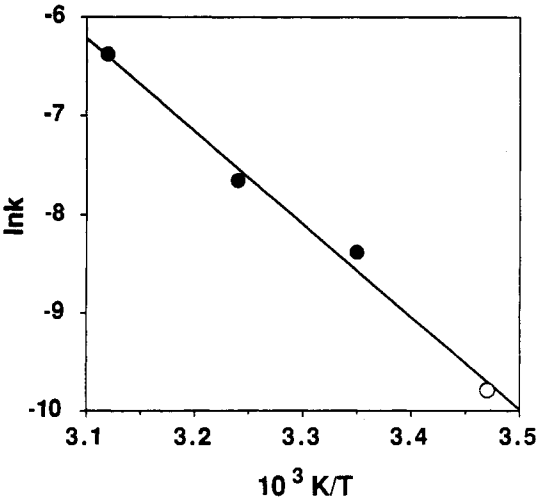


Figure 3. Arrhenius plot for racemization of (+)-$MeMPA^+X^-$: (○) X = I; (●) X = (+)-camphorsulfonate (r = 0.996, sd = 0.1356).

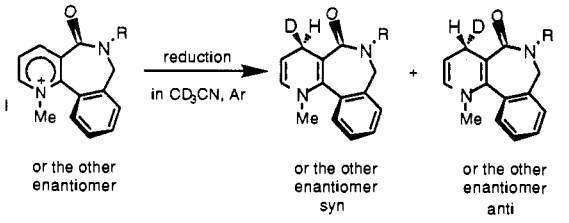
at the C_4 position (syn and anti to the carbonyl oxygen[21]). Therefore, the stereochemistry associated with the reduction of $MeMPA^+$ with a deuterated reagent can be monitored quite easily. The results are summarized in Table 3 together with those of $BuMPA^+$. It is interesting to note that a (net) hydride originating from BNAH or its analog attacks $MeMPA^+$ from the side of the pyridinium ring where the carbonyl oxygen lies, even though this is the more sterically hindered face. Thus, the stereochemistry of the reaction cannot be explained as a steric effect, and there is no doubt that the carbonyl dipole or an electronic effect plays an important role in determining the stereochemical outcome of the reaction.

The stereochemical result of the reduction with sodium dithionite in D_2O affords a syn/anti ratio[21] of 50/50, which is different from those with BNAH and its analogs. However, we must point out the possibility that the compound has undergone racemization during the processes of isolation and spectroscopy. Indeed, a preliminary result from the reduction of 6,7-dihydro-6-methyl-5-oxopyridino[3,2-*d*]-2-(3-methylbenz)azepin (3Me-$MeMPA^+$), the conformation of which is stable at room temperature, in contrast to the unstability of those of $MeMPA^+$ and $BuMPA^+$, with sodium dithionite has revealed that the syn/

(20) Cullen, K. E., Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2961–2967.

(21) Syn- and anti-hydrogens denote those occupying the same face as the carbonyl oxygen and the other faces, respectively.

Table 3. Reduction of a Racemic Mixture of *N*-Methylpyridinium from 6,7-Dihydro-6-methyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepin ($MeMPA^+$) and 6,7-Dihydro-6-*tert*-butyl-5-oxo-*N*-methylpyridino[3,2-*d*]-2-benzazepin ($BuMPA^+$)[a]



pyridinium	time, h	reducing reagent	stereochemistry[b,c] syn:anti
$MeMPA^+$	1.0	$Na_2S_2O_4/D_2O$	50:50
(R = Me)	39[d]	BNAH-4,4-d_2	65:35
	1.5	(*R*)-Me_2PNPH-4-*d*	58:42
	1.5	(*S*)-Me_2PNPH-4-*d*	60:40
$BuMPA^+$	1.0	$Na_2S_2O_4/D_2O$	51:49
(R = ^{t}Bu)	39[d]	BNAH-4,4-d_2	67:33
	1.5	(*R*)-Me_2PNPH-4-*d*	70:30
	1.5	(*S*)-Me_2PNPH-4-*d*	69:31

[a] About 20% of MeMPAD or BuMPAD initially produced by the reduction reacts with $MeMPA^+$ or $BuMPA^+$, respectively, yielding 4,4-dihydro and 4,4-dideuterio compounds. [b] Relative to the carbonyl oxygen. [c] Estimated error is about ±3 for all numbers. [d] Reaction at 35 °C.

anti ratio is 80/20.[22] Further investigation is necessary before a conclusion is formed on the stereochemical difference between hot and cold reducing agents.

It has been proposed that the carbamoyl moiety in an NADH analog faces a polar side chain of the substrate or oxidizing agent at the transition state of a homogeneous reaction.[23] Magnesium ion promotes this face-to-face interaction by coordinating on itself both reducing and oxidizing agents.[24] Not only is the stereochemistry improved by the sandwich-like interaction of magnesium ion, but the reaction rate is also increased by its catalytic effect. The present reaction, however, is retarded by the presence of magnesium ion, which is quite reasonable because one of the agents is an onium, and it is highly plausible that a cation is hardly coordinated on a cationic magnesium ion. Thus, a binary complex between the reducing and oxidizing agents is a plausible intermediate in the present reaction even in the presence of magnesium ion.

The fact that both (4*R*)- and (4*S*)-Me_2PNPD afford the same syn/anti ratio within experimental error confirms the idea that face-to-face interaction between the carbonyl group in the onium and the one in the reducing agent is important at the transition state of the reaction, as proposed previously.[14]

To our best knowledge, the $MeMPA^+$/MeMPAH system is the first example of molecular asymmetry stemming from the orientation of the carbonyl group only and resolved to each enantiomer.

The present result strongly supports the possibility of a functional model for chemical evolution of an enzyme, in which it is predicted that $NAD(P)^+$/NAD(P)H coenzymes themselves can induce chirality in an achiral substrate during a redox reaction without stereochemical assistance of a protein.[25]

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Supplementary Material Available: Crystallographic data, tables of atomic positional and thermal parameters, and bond lengths and angles for the (+)-camphorsulfonate salt of $MeMPA^+$ (18 pages); listing of observed and calculated structure factors (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(22) Ohno, A.; Tsutsumi, A.; Yamazaki, N.; Mikata, Y.; Okamura, M. Unpublished result (1994).
(23) Ohno, A.; Goto, T.; Nakai, J.; Oka, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3478–3481.
(24) Ohno, A.; Kimura, T.; Yamamoto, H.; Kim, S. G.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1535–1538.
(25) Ohno, A. *Proc. 14th Int. Cong. Biochem., Prague* **1989**, *2*, 217–223.