NAD(P)$^+$–NAD(P)H Models. 87. Nonsteric Stereochemistry Controlled by a Carbonyl Dipole

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6,7-Dihydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin-1-ium iodide (11-Me-MMPA$^+$I$^-$) was synthesized, and it was confirmed that the axial chirality in the salt is stable at room temperature. Upon the reduction of 11-Me-MMPA$^+$ with a pair of diastereomeric dihydropyridine derivatives, the reacting face is always that in which the carbonyl dipole in the cation is included (i.e., syn selectivity), regardless the configuration of the reducing agent. A steric hindrance, in a classical sense, and other factors contribute to the stereochemistry of the reaction only in a minor part. Plausible intermolecular arrangements at the transition state of the reaction are discussed in order to understand the mechanism of this nonsteric stereochemistry.

It was reported that the stereochemistry associated with the oxidation of *N*,2,4-trimethyl-*N*-(α-methylbenzyl)-1-propyl-1,4-dihydronicotinamide (Me_3PNPH) and 1,2,4-trimethyl-3-[*N*-methyl-*N*-(α-methylbenzyl)carbamoyl]-1,4-dihydroquinoline (Me_3MQPH) is controlled by the orientation of the carbonyl dipole in the side-chain amide group (Chart 1).[1,2] The stereochemistry also depends on the reactivity of an oxidizing agent: In a series of reactions with 1,4-benzoquinone derivatives the less reactive agent abstracts the hydrogen *syn* to the carbonyl oxygen more easily than the other:[1] A weaker base employed as a catalyst for electrochemical oxidation prefers to react with the same *syn*-hydrogen.[2] As the reaction conditions become stronger (stronger oxidizing agents or bases), the *anti*-hydrogen tends to react preferentially.

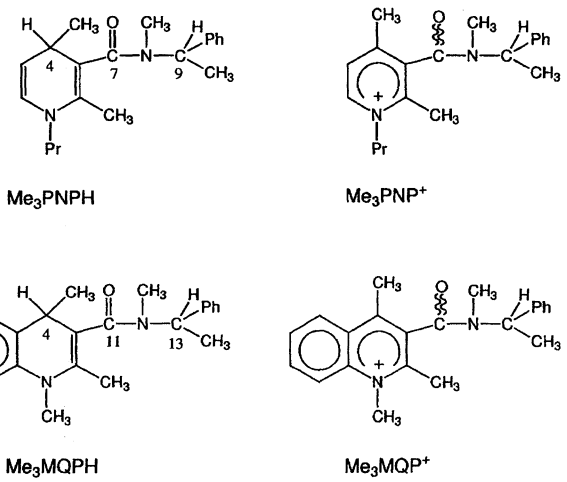


Chart 1.

The observations are parallel to those discovered in biological systems, as summarized by Nambiar et al.,[3] and the mechanism is worth studying in relation to the chemical evolution of enzymes. The observation is also new from the viewpoint of physical organic chemistry, where the stereochemical results have been interpreted only in terms of the relative bulkiness of the substituents. The phenomenon in which the orientation of a dipole, instead of the relative bulkiness of substituents, controls the stereochemistry of the reaction is called the *nonsteric stereochemistry*.

Both Felkin-Anh[4,5] and Cieplak[6] models are famous for predicting a preferentially reactive face of a carbonyl group. However, since the models have always been interpreted in terms of an inherent property of the carbonyl compound, ignoring the property of an attacking nucleophile, they are unable to predict a stereochemical reversion which depends on the reactivity of the nucleophile.

We now know that the stereochemical course is not an absolute, or inherent, property of the carbonyl compound, but is defined by a relative property (reactivity) with respect to the attacking nucleophile. Thus, the mechanism of stereocontrol mediated by the orientation of a substituent dipole has been extensively studied, and is interpreted in terms of the participation of an encounter complex between the reducing and oxidizing agents formed in advance of the chemical reaction.[7]

Since both Me_3PNP^+/Me_3PNPH and Me_3MQP^+/Me_3MQPH couples have central chiralities at the side-chain α-meth-

ylbenzyl groups, or are diastereomeric, there still remains an ambiguity in these systems that the chirality at the α-methylbenzyl group might contribute to the stereochemistry of the reaction. At the same time, it was proposed that the α-methylbenzyl group might occupy the opposite face from that occupied by the carbonyl oxygen, interfering a dissociation of the transferring hydrogen in this face.[8] In order to avoid any unnecessary ambiguity, we synthesized the following new compounds: 6,7-dihydro-1,6-dimethyl-5-oxo-5*H*-benzo[*c*]-pyrido[2,3-*e*]azepin-1-ium iodide (MMPA$^+$I$^-$) and its *t*-butyl analog, 6-*t*-butyl-6,7-dihydro-1-methyl-5-oxo-5*H*-benzo[*c*]-pyrido[2,3-*e*]azepin-1-ium iodide (BMPA$^+$I$^-$), where no extra, unnecessary central chirality exists (Chart 2).[9] However, unfortunately, since conformations of these new molecules are not sufficiently stable to keep their axial chiralities at room temperature, racemization takes place at a moderate velocity, thus making it difficult to accurately follow the stereochemistry of the reaction. In addition, their corresponding reduced forms, MMPAH and BMPAH, are so unstable that studies on the stereochemistry in the oxidation of these compounds were unsuccessful.

To obtain a conformationally stable compound, we next designed 6,7-dihydro-1,6,11-trimethyl-5-oxo-5*H*-benzo-[*c*]pyrido[2,3-*e*]azepin-1-ium iodide (11-Me-MMPA$^+$I$^-$), where the methyl substituent at the 11-position in an *o*-phenylene group prevents a flipping of the *o*-phenylene moiety, and, therefore, a flipping of the carbonyl group at room temperature. At the same time, it was found that the corresponding reduced form, 11-Me-MMPAH, is sufficiently stable to be isolated from the reaction mixture after reduction. In this paper we wish to report on the stereochemistry associated with the reduction of 11-Me-MMPA$^+$I$^-$ in order to emphasize that the orientation of the carbonyl dipole is the major factor in controlling the stereochemistry of the reaction (Scheme 1). Plausible configurations of the encounter complex are also described.

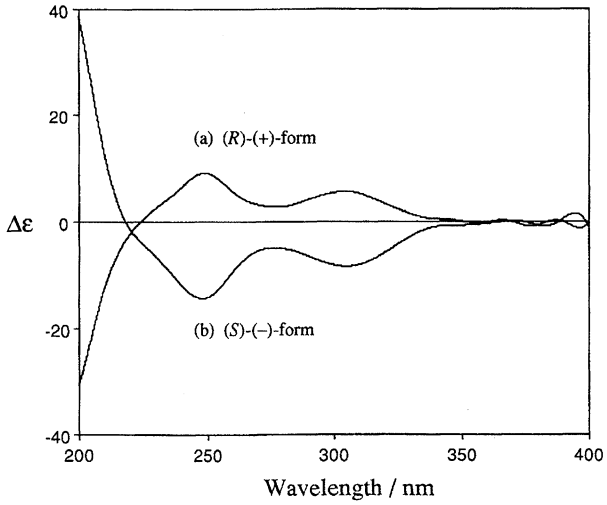


Fig. 1. CD spectra of (a) (*R*)-(+)- and (b) (*S*)-(−)-11-Me-MMPA$^+$I$^-$ in MeOH.

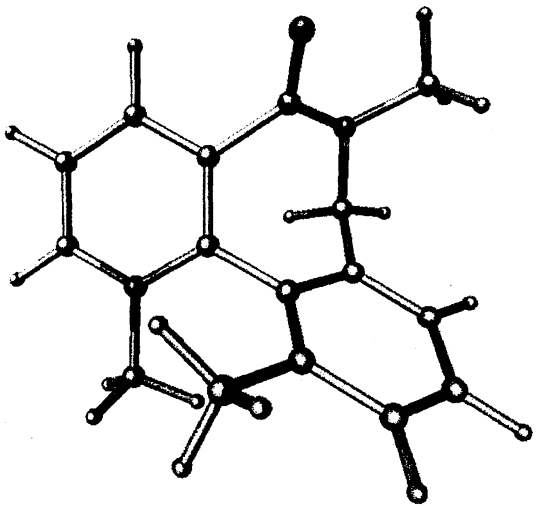


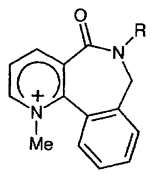
Fig. 2. Conformation of (*R*)-(+)-11-Me-MMPA$^+$ elucidated by PM3 calculation with MNDO94 program.

Results

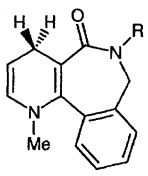
Preparation and Optical Resolution of 11-Me-MMPA$^+$I$^-$. A racemic mixture of 11-Me-MMPA$^+$I$^-$ was synthesized according to a similar procedure as previously reported.[9] The reaction conditions and chemical yields of the products are summarized in Scheme 2 together with those for the reduction of 11-Me-MMPA$^+$I$^-$.

The counter anion of the racemic salt was changed from iodide to trifluoroacetate, and the salt was subjected to preparative HPLC on Daicel CHIRALCEL OD at room temperature with C_6H_{14}/EtOH/MeOH/$Et_2NH_2^+CF_3CO_2^-$ = 85/10/5/0.1 (v/v/v/w) as an eluent.

In order to separate the chiral salt from $Et_2NH_2^+CF_3CO_2^-$ contamination, the former salt was reduced by $Na_2S_2O_4$ in a benzene/phosphate buffer (pH = 7.5) system. Subsequently, the reduced form, 11-Me-MMPAH, was oxidized by chloranil to 11-Me-MMPA$^+$, and the thus-obtained salt was treated by an anion-exchangeable resin (iodide form of

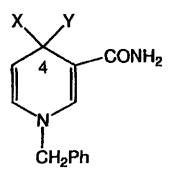


R=Me : MMPA$^+$
R=^{t}Bu : BMPA$^+$

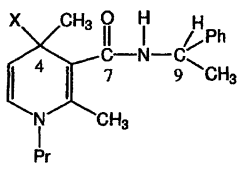


R=Me : MMPAH
R=^{t}Bu : BMPAH

Chart 2.

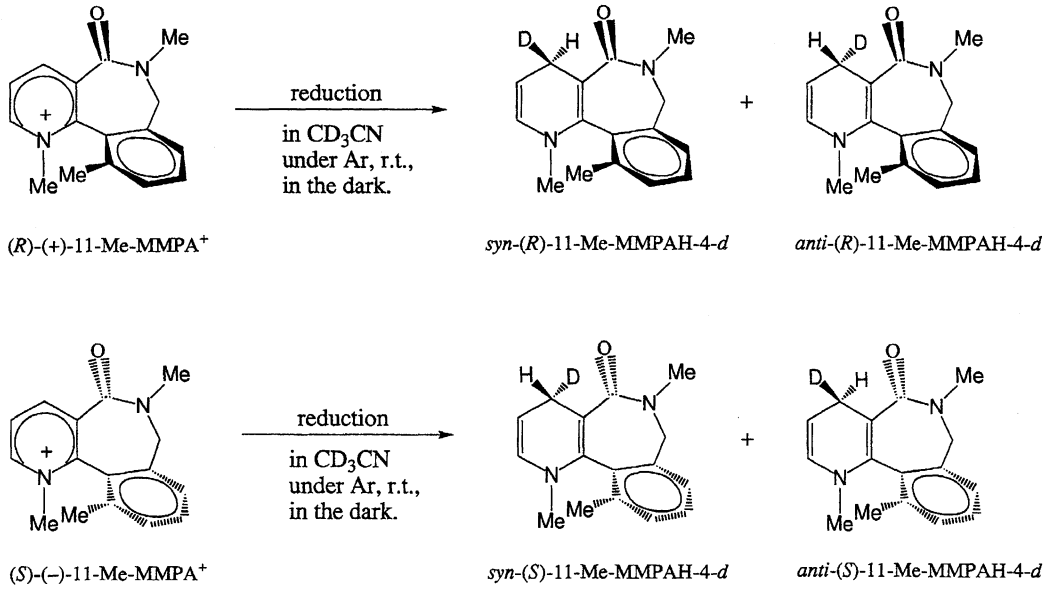


X=H, Y=H : BNAH
X=D, Y=D : BNAH-4-4-d_2

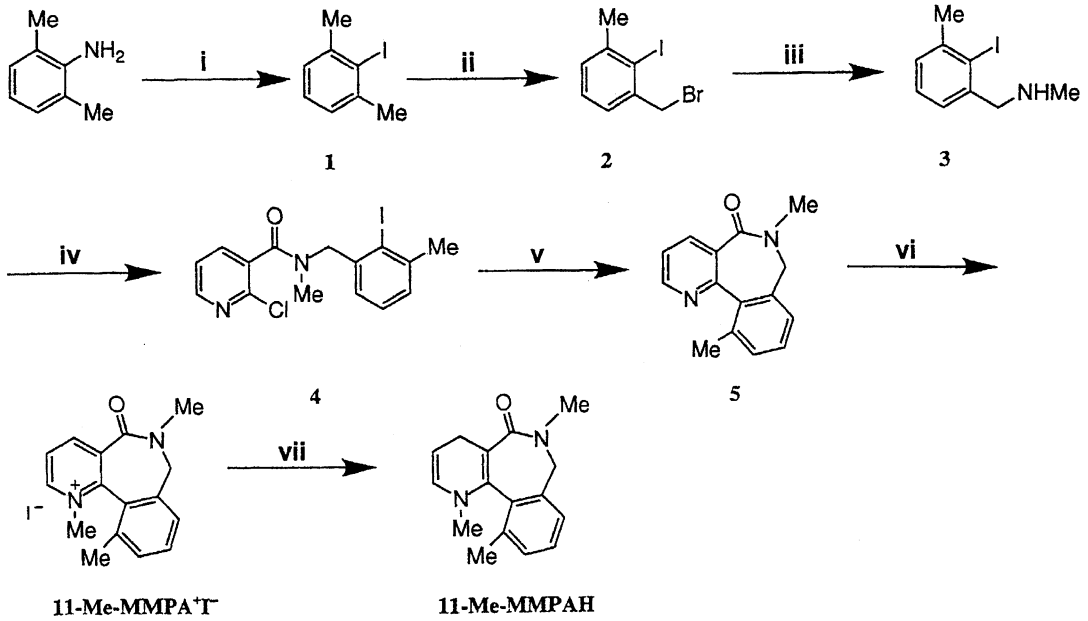


X=H : Me_2PNPH
X=D : Me_2PNPH-4-*d*

Chart 3.



Scheme 1.



Scheme 2. Reagents and conditions: (i) HCl, $NaNO_2$, KI, 0 °C-room temperature (r.t.), 48% yield; (ii) NBS, AIBN, CCl_4, reflux, 10 h, 54% yield; (iii) $MeNH_2$/MeOH, r.t., 3 h, 68% yield; (iv) 2-Chloronicotinic acid, $SOCl_2$, reflux, 1 h, EtOAc, r.t., 2 h, 69% yield; (v) Zn, $NiBr_2(PPh_3)_2$, Et_4NI, THF, r.t., 1 h, 77% yield; (vi) MeI, CH_3CN, 70 °C, 24 h, 90% yield; (vii) $Na_2S_2O_4$, buffer/CH_2Cl_2, r.t., 2 h, 79% yield.

IRA-400) at room temperature. The thus-obtained (+)- and (−)-11-Me-MMPA$^+$I$^-$ have $[\alpha]_D^{25}$ +188° (c=0.550, MeOH) and $[\alpha]_D^{25}$ −195° (c=0.550, MeOH), respectively. The CD spectra of both enantiomers are shown in Fig. 1.

The Cotton effect in (+)-11-Me-MMPA$^+$ observed here is the same as that in the previously reported[9] (*R*)-(+)-MMPA$^+$, which predicts that the absolute configuration of (+)- and (−)-11-Me-MMPA$^+$ might be *R* and *S*, respectively. A detailed procedure for assigning the absolute configuration of 11-Me-MMPA$^+$ is given in the next section.

Absolute Configuration of 11-Me-MMPA$^+$. The absolute configuration of 11-Me-MMPA$^+$ has not yet been elucidated. However, an X-ray crystallographic result has revealed that (+)-MMPA$^+$ has an *R* configuration, and that the conformation elucidated by a PM3 calculation with the MNDO94 program coincides excellently with that obtained by X-ray crystallography.[10] A molecular orbital-calculation for 11-Me-MMPA$^+$ with the same program predicts that the stable conformation of 11-Me-MMPA$^+$ does not deviate appreciably from that of MMPA$^+$.[11] These facts guarantee the expectation that the conformation of 11-Me-MMPA$^+$, elucidated by a PM3 calculation, and shown in Fig. 2, might safely be believed to be correct. Thus, with the aid of the coincidence of the CD spectra, the absolute configuration of the cation can be assigned to be the same as that of MMPA$^+$, or (+)-11-Me-MMPA$^+$ has an *R* configuration. The following

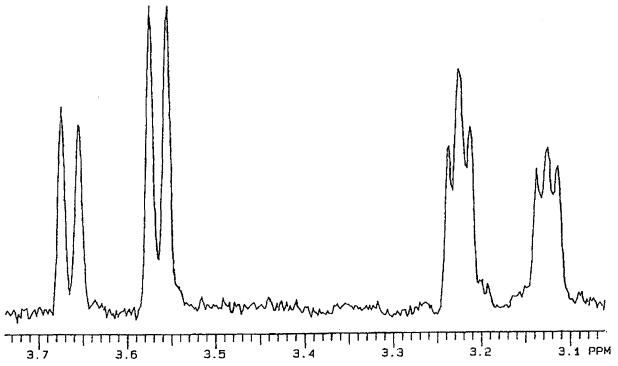


Fig. 3. A part of ^{1}H NMR spectrum of 11-Me-MMPAH in CD_3CN.

discussion is based on this tentatively assumed conformation.

^{1}H NMR Spectrum of 11-Me-MMPAH. The ^{1}H NMR spectrum of 11-Me-MMPAH exerts two completely separated signals at $\delta = 3.17$ (ddd) and 3.61 (dd), stemming from *anti* and *syn* methylene protons,[12] respectively, at the C_4 position (Fig. 3). The relative areas of these signals were compared with each other in order to elucidate the *anti* : *syn* reactivity ratio.

Reduction of 11-Me-MMPA$^+$I$^-$. Racemic 11-Me-MMPA$^+$I$^-$ was reduced by $Na_2S_2O_4$ in D_2O (a phosphate buffer) at room temperature in the dark under an argon atmosphere for 5 h. Signals from the *anti*- and *syn*-hydrogens in ^{1}H NMR spectrum of the reaction product appeared in a 80 : 20 ratio of the integrated areas, revealing that a deuterium attack on the cation takes place in its *anti* and *syn* faces with a ratio of 20 : 80. Although the reaction with BNAH-4,4-d_2 in CD_3CN was too slow to be followed, the reaction with the more reactive Me_2PNPH-4-*d* proceeded smoothly to give a product in a similar *anti* : *syn* ratio (Chart 3). It was a surprise that combinations of (4*R*,9*R*)-Me_2PNPH-4-*d* and (4*S*,9*S*)-Me_2PNPH-4-*d* with (*R*)-(+)-11-Me-MMPA$^+$, respectively, and vice versa, afforded the products in almost the same configurational ratio. Thus, in all cases, the *syn*-face is more reactive than the other. The results are summarized in Table 1.

Table 1. Stereoselectivity in the Reduction of (*R*)-(+)- and (*S*)-(−)-6,7-Dihydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin-1-ium Iodide (11-Me-MMPA$^+$I$^-$) under the Control of Dipole Orientation

Config. of 3-Me-MMPA$^+$	Reducing agnet	Solvent	Stereoselectivity[a] *anti* : *syn*
Racemic	$Na_2S_2O_4$	D_2O[b]	20 : 80
	(4*S*,9*S*)-Me_2PNPH-4-*d*	CD_3CN	25 : 75
	(4*R*,9*R*)-Me_2PNPH-4-*d*	CD_3CN	22 : 78
(*R*)-(+)	(4*S*,9*S*)-Me_2PNPH-4-*d*	CD_3CN	25 : 75
	(4*R*,9*R*)-Me_2PNPH-4-*d*	CD_3CN	29 : 71
(*S*)-(−)	(4*S*,9*S*)-Me_2PNPH-4-*d*	CD_3CN	28 : 72
	(4*R*,9*R*)-Me_2PNPH-4-*d*	CD_3CN	24 : 76

a) Errors are ±2.0. b) In phosphate buffer (D_2O)/CH_2Cl_2.

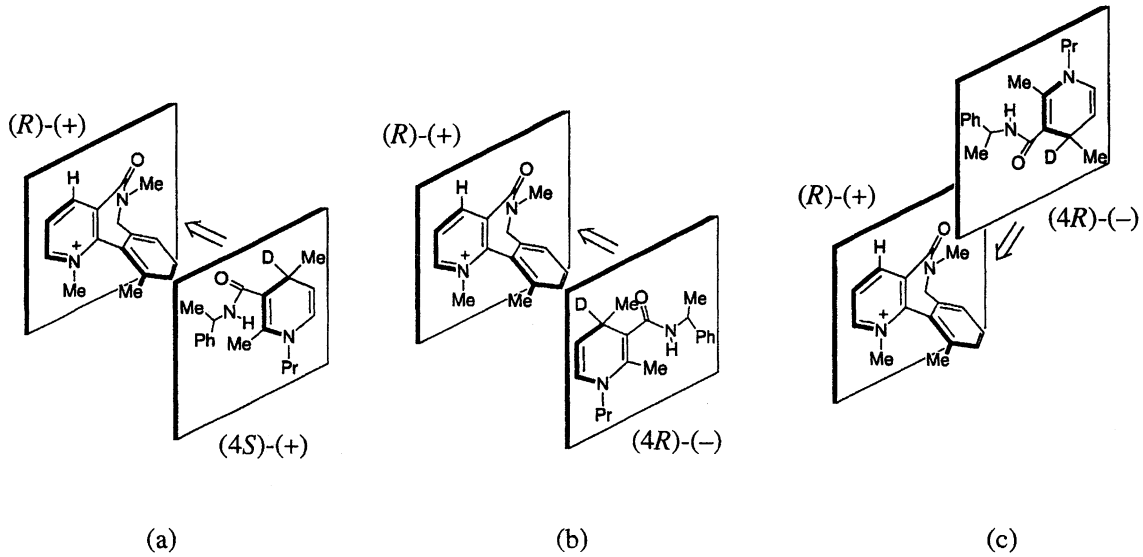


Fig. 4. Intermolecular arrangements of the encounter complex (or the transition state) to the *syn* product: (a) *endo-trans*, (b) *endo-cis*, and (c) *exo-trans* configurations.

Discussion

The results reveal that the molecular face which includes the carbonyl dipole is more reactive than the other (i.e., *syn* selectivity) toward the reduction, despite the fact that this particular face is sterically interfered, if any, by the carbonyl group and a bulky *o*-phenylene moiety. In other words, when the classical idea of stereochemistry is taken into consideration, this face should be less reactive than the other, because of the steric hindrance caused by the *o*-phenylene and carbonyl moieties. It has been experimentally proven that this expectation, based on the classical idea, is not correct.

That both enantiomers of the reducing agent afford the same *syn* selectivity proves that the stereochemical course oriented by the intramolecular dipole overwhelms the course predicted by the classical idea of a steric hindrance in the present reaction system.

The syn selectivity in the combination of (4*S*,9*S*)-Me_2PNPH-4-*d* and (*R*)-(+)-11-Me-MMPA$^+$, for example, is reasonable, because the *endo-trans-syn* configuration[12] is assigned to the encounter complex (or the transition sate) of the reaction (Fig. 4a). This intermolecular arrangement can satisfy both the dipolar and classical steric requirements in addition to the electron-transfer π–π stacking contribution, resulting in the *endo* arrangement.[13,14] On the other hand, the encounter complex (or the transition state) in a reaction from a combination of (4*R*,9*R*)-Me_2PNPH-4-*d* and (*R*)-(+)-11-Me-MMPA$^+$ must assume either the *endo-cis-syn* (Fig. 4b) or *exo-trans-syn* (Fig. 4c) configuration. The *endo* arrangement must inevitably be associated by the *cis* configuration. However, since, as mentioned initially, the *syn* face is very much crowded because of the bulky *o*-phenylene group, it seems unlikely that the sterically more crowded side of the reducing agent is set against this crowded group. It should be noted that the carbonyl oxygen in Me_2PNPH is fixed at the *syn* conformation when the (net) hydride is transferred from this molecule to a pyridinium cation.[14] Thus, the local area around the reaction center is expected to be highly crowded when the *endo* arrangement is chosen by the reacting molecules. Consequently, we propose that the transition state of the reaction assumes the *exo-trans-syn* arrangement (Fig. 4c).

The present system is the first to propose an *exo* arrangement for the series of reactions being presently discussed. Mentioning this is necessary for this proposal. All of the facts: (1) that both $Na_2S_2O_4$ and Me_2PNPH-4-*d* result in a similar *anti* : *syn* ratio of 20 : 80,[15] (2) that BNAH is unable to reduce this cation in contrast to its mother compound, MMPA$^+$, and (3) that MMPA$^+$ reacts with 3 molar amounts of Me_2PNPH-4-*d* within 1.5 h, whereas it takes 3 h for 11-Me-MMPA$^+$ to complete the reaction, predict that the methyl substituent on the *o*-phenylene moiety reduces the reactivity of the cation appreciably. Since it is implausible to expect that the methyl group exerts such a large electronic effect, there is no doubt that the methyl group, which sticks out of the *o*-phenylene group, so as to cover the pyridinium-cation center, prevents the reducing agent from approaching in this face to form an encounter complex. In other words, unlike other systems that we have so far treated, the present pyridinium/dihydropyridine couple has a structure that is sterically difficult to form the encounter complex through an electron-transfer π–π stacking interaction. However, the π–π stacking interaction is so dominant over the classical steric effect that it operates to form the *endo* arrangement, where the *trans* configuration appreciably reduces the steric repulsion. We thus believe that the *endo*/*exo* (the presence or absence of the π–π stacking interaction) and *trans*/*cis* (the presence or absence of the classical steric effect) arrangement balance each other, depending on the structures of the reducing and oxidizing agents.

The fact that each pair affords the same *anti* : *syn* ratio predicts that the facilities of the reactions through the *endo* and *exo* transition states are almost equivalent, because of a cancellation of the favorable and unfavorable effects. In any case, it is conceivable that the carbonyl dipole plays a role to attract the reacting counterpart from the face that it exists in. Such a strong control of the stereochemistry by an electronic (nonsteric) effect may be a mimic of stereochemical controls in biological reactions catalyzed by archaic enzymes, where structural sophistication was insufficient to exert a perfect control of the stereochemistry.[16]

There still remains a small possibility, however, that the conformational rigidity introduced to the cation by this methyl group plays a large role in the reduction of reactivity. Whichever the mechanism is, we unfortunately failed to find such a reactive reducing agent so as to exemplify the variation, or reversion, of the reactivity ratio in the reduction of 11-Me-MMPA$^+$.

Experimental

Instruments. Melting points were obtained on a Yanagimoto micro melting-point apparatus and were uncorrected. The ^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR 200 FT-NMR spectrometer. Infrared spectra were collected on a JACSO FT/IR-5300 spectrometer. Elemental analyses were performed with a Yanaco MT-3 elemental analyzer. Optical rotations were measured on a JASCO DIP-181 polarimeter. Circular dichroism spectra were collected on a JASCO J-720W spectropolarimeter.

Materials. 2-Chloronicotinic acid was purchased from Tokyo Kasei Co., Ltd., 2,6-dimethylaniline from Nacalai Tesque Co., Ltd., and IRA-400 anion-exchangeable resin from Organo Co., Ltd. THF was freshly distilled from sodium benzophenone ketyl immediately prior to use. CH_3CN was freshly distilled from CaH_2 prior to use. All other chemicals were of reagent grade, and were used without purification. Column chromatography was performed with silica-gel 60 (Nacalai Tesque, 70—230 mesh) or alumina 90 active basic (Merck, 70—230 mesh).

A buffer was prepared with KH_2PO_4 and NaOH to be pH 7.5, and degassed prior to use.

A standard work-up means that the organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure.

Preparation of 2,6-Dimethyliodobenzene (1). Concd HCl (150 mL) and 2,6-dimethylaniline (38.7 g, 0.32 mol) were placed in a 500 mL Erlenmeyer flask containing a magnetic stirring bar. After being stirred for a while, 100 g of ice was added to the mixture,

cooled in an ice-salt bath; then, a solution of $NaNO_2$ (24.3 g, 0.35 mol) in H_2O (100 mL) was added dropwise to the mixture at 0—5 °C. After being stirred for 15 min, the solution was slowly poured into a solution of KI (180 g, 1.08 mol) in H_2O (600 mL); the whole mixture was kept at room temperature overnight to yield a heavy dark oil. To the mixture were added aqueous NaOH and hexane. The organic layer was separated, and the organic materials in the aqueous layer were extracted with hexane several times. The combined organic layer was subjected to the standard work up. The obtained residue was purified by column chromatography on silica gel with hexane as an eluent to afford 35.3 g of **1** as a colorless oil: Yield 48%; IR (Neat) 2974, 1456, 1006, 767, 555 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.46 (s, 6H, CH_3), 7.01—7.15 (m, 3H, arom.). Anal. Found: C, 41.67; H, 3.96%. Calcd for C_8H_9I: C, 41.40; H, 3.91%.

Preparation of 2-Bromomethyl-6-methyliodobenzene (2). *N*-Bromosuccinimide (23.1 g, 0.13 mol) and α,α'-azobisisobutyronitrile (0.2 g, 0.001 mol) were added to a solution of **1** (29.5 g, 0.12 mol) in dry CCl_4 (300 mL); the mixture was then refluxed for 10 h under an argon atmosphere. Precipitated succinimide was removed by filtration, and the filtrate was poured into saturated aqueous $Na_2S_2O_3$. The organic layer was separated and worked-up by the standard procedure. The residue was subjected to column chromatography on silica gel with hexane as an eluent to afford 20.2 g of **2** as a colorless oil: Yield 54%; IR (Neat) 2974, 1435, 1012, 783, 619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.49 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 7.12—7.31 (m, 3H, arom.); EIMS *m/z* (rel intensity) 310 (M^+; 20), 231 (100), 103 (31), 7 (21).

Preparation of *N*-(2-Iodo-3-methylbenzyl)methylamine (3). Methylamine (40% in MeOH, 30 mL) was placed into a 100 mL, round-bottomed, three-necked flask equipped with a magnetic stirring bar and a dropping funnel. Subsequently, **2** (20 g, 0.064 mol) dissolved in MeOH (30 mL) was added to the solution dropwise. The reaction mixture was stirred for 3 h at room temperature. After the solvent was evaporated from the mixture under reduced pressure, H_2O and EtOAc were added to the obtained residue with stirring. The organic layer was separated and worked-up by the standard procedure. The residue was purified by column chromatography on silica gel with EtOAc as an eluent to afford 10.6 g of **3** as a colorless oil: Yield 68%; IR (Neat) 3317, 2943, 1446, 1006, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.45 (s, 3H, N-CH_3), 2.48 (s, 3H, 3-CH_3), 3.81 (s, 2H, CH_2), 7.10—7.21 (m, 3H, arom.); EIMS *m/z* (rel intensity) 261 (M^+; 80), 134 (100), 118 (17), 104 (22), 91 (29), 77 (31).

Preparation of 2-Chloro-3-[*N*-(2-iodo-3-methylbenzyl)-*N*-methylcarbamoyl]pyridine (4). In a 200 mL, round-bottomed, three-necked flask equipped with a magnetic stirring bar and a reflux condenser protected by an alkaline trap, a mixture of 2-chloronicotinic acid (3.6 g, 23 mmol) and $SOCl_2$ (30 mL, 410 mmol) was refluxed for 1 h. The solution turned brown. After excess $SOCl_2$ was removed by distillation under reduced pressure, a brown residue was obtained. Et_3N (20 mL) dissolved in EtOAc (50 mL) was poured onto the residue cooled in an ice bath with stirring. Subsequently, **3** (6.9 g, 26 mmol) dissolved in EtOAc (50 mL) was added to the solution in an ice bath for over 30 min dropwise. After the reaction mixture had been stirred for 2 h at room temperature, H_2O (100 mL) was added. The organic layer was separated and worked-up with the standard procedure. The residue was subjected to column chromatography on silica gel with EtOAc used as an eluent to afford crude **4**, which was then recrystallized from MeOH to afford 7.2 g of pure **4** as colorless crystals: Yield 69%; mp 147.0—147.5 °C; IR (KBr) 1643, 1394, 1305, 1103, 1059, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$) *E*/*Z* = 3/2.

(*E*)-form: δ = 2.51 (s, 3H, 3′-CH_3), 2.83 (s, 3H, N-CH_3), 4.91 (bs, 2H, CH_2), 7.18—7.27 (m, 3H, arom.), 7.35 (dd, $J_{4,5}$ = 7.6, $J_{5,6}$ = 4.8 Hz, 1H, C5-H), 7.75 (dd, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.9 Hz, 1H, C4-H), 8.47 (dd, $J_{5,6}$ = 4.8, $J_{4,6}$ = 1.9 Hz, 1H, C6-H).

(*Z*)-form: δ = 2.43 (s, 3H, C3′-CH_3), 3.13 (s, 3H, N-CH_3), 4.42 (s, 2H, CH_2), 6.98 (m, 1H, arom.), 7.18—7.27 (m, 3H, C5-H and arom.), 7.57 (m, 1H, C4-H), 8.40 (m, 1H, C6-H). Anal. Found: C, 44.95; H, 3.47; N, 6.94%. Calcd for $C_{15}H_{14}N_2IClO$: C, 44.96; H, 3.52; N, 6.99%.

Preparation of 6,7-Dihydro-6,11-dimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepine (5). Into a 100 mL, round-bottomed, two-necked flask containing a magnetic stirring bar, $NiBr_2(PPh_3)_2$ (0.928 g, 1.25 mmol), zinc powder (0.408 g, 6.25 mmol), and Et_4NI (0.321 g, 1.25 mmol) were placed. The flask was degassed and filled with argon several times. Dry THF (15 mL) was added through a syringe, and the mixture was stirred at room temperature. After the reddish brown catalyst had formed (5 min), an argon-purged solution of **4** (0.501 g, 1.25 mmol) in THF (30 ml) was slowly added through a syringe. The reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was poured into 2 M aqueous NH_3 (50 mL), and Et_2O (50 mL) was added (1 M = 1 mol dm^{-3}). The mixture was filtered and the organic layer separated. The organic materials in the aqueous layer was extracted with Et_2O several times. The combined organic layer was evaporated under reduced pressure. The residue was extracted with 1 M HCl (50 mL) twice, and the combined extract was neutralized with aqueous NaOH to produce a white precipitate. The collected precipitate was recrystallized from Et_2O to afford 0.23 g of **5** as white crystals: Yield 77%; mp 145.0—146.0 °C; IR (KBr) 1637, 1408, 790, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.46 (s, 3H, C11-CH_3), 3.16 (s, 3H, N6-CH_3), 3.84 (d, ^2J = 15 Hz, 1H, CH_2), 4.41 (d, ^{2} = 15 Hz, 1H, CH_2), 7.14 (m, 1H, arom.), 7.26—7.31 (m, 2H, arom.), 7.38 (dd, $J_{3,4}$ = 7.8, $J_{2,3}$ = 4.7 Hz, 1H, C3-H), 8.25 (dd, $J_{3,4}$ = 7.8, $J_{2,4}$ = 1.8 Hz, 1H, C4-H), 8.77 (dd, $J_{2,3}$ = 4.7, $J_{2,4}$ = 1.8 Hz, 1H, C2-H). Anal. Found: C, 75.87; H, 5.92; N, 11.71%. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.75.

Preparation of 6,7-Dihydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin-1-ium Iodide (11-Me-MMPA$^+$I$^-$). MeI (1.78 g, 12.6 mmol) in CH_3CN (10 mL) and **5** (0.300 g, 1.26 mmol) were placed in a 50 mL, round-bottomed flask equipped with a reflux condenser protected with a tube of $CaCl_2$. The reaction mixture was stirred for 24 h at 70 °C in the dark. The solution turned yellow. After the solvent had been evaporated from the mixture under reduced pressure, a yellow residue was obtained. This residue was washed with hexane several times and dried under reduced pressure. Recrystallization of the residue from EtOH afforded 0.43 g of 11-Me-MMPA$^+$I$^-$ as yellow crystals: Yield 90%; mp 185.0—185.5 °C; IR (KBr) 3422, 1639, 1487, 1402, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.22 (s, 3H, C11-CH_3), 3.10 (s, 3H, N6-CH_3), 3.93 (d, ^2J = 15 Hz, 1H, CH_2), 4.44 (s, 3H, N1-CH_3), 5.33 (d, ^2J = 15 Hz, 1H, CH_2), 7.33—7.58 (m, 3H, arom.), 8.18 (dd, $J_{3,4}$ = 8.0, $J_{2,3}$ = 6.2 Hz, 1H, C3-H), 8.78 (dd, $J_{3,4}$ = 8.0, $J_{2,4}$ = 1.6 Hz, 1H, C4-H), 9.54 (dd, $J_{2,3}$ = 6.2, $J_{2,4}$ = 1.6 Hz, 1H, C2-H). Anal. Found: C, 48.25; H, 4.53; N, 6.90%. Calcd for $C_{16}H_{17}N_2IO\cdot H_2O$: C, 48.25; H, 4.80; N, 7.03%.

Preparation of 1,4,6,7-Tetrahydro-1,6,11-trimethyl-5-oxo-5*H*-benzo[*c*]pyrido[2,3-*e*]azepin (11-Me-MMPAH). Into a 10 mL round-bottomed flask, was placed 11-Me-MMPA$^+$I$^-$ (21.9 mg, 0.052 mmol) dissolved in a buffer (2.5 mL). After CH_2Cl_2 (2.5 mL) was added through a syringe with stirring, $Na_2S_2O_4$ (18.3 mg, 0.105 mmol) dissolved in a buffer (2.5 mL) was added through a syringe. After the reaction mixture was stirred for 2 h at room

temperature under an argon atmosphere in the dark, the organic layer was separated and subjected to the standard work-up procedure. Immediately, the residue was subjected to column chromatography on alumina with CH_2Cl_2 as an eluent to afford 10.5 mg of 11-Me-MMPAH as a pale-yellow paste: Yield 79%; ^{1}H NMR (CD_3CN) δ = 2.40 (s, 3H, C11-CH_3), 2.63 (s, 3H, N1-CH_3), 2.92 (s, 3H, N6-CH_3), 3.17 (ddd, ^2J = 20, $J_{3,4e}$ = 2.9, $J_{2,4e}$ = 2.0 Hz, 1H, C4-H_e), 3.61 (dd, ^2J = 20, $J_{3,4a}$ = 4.0 Hz, 1H, C4-H_a), 3.95 (d, ^2J = 14 Hz, 1H, CH_2), 4.72 (d, ^2J = 14 Hz, 1H, CH_2), 4.84 (ddd, $J_{2,3}$ = 7.7, $J_{3,4a}$ = 4.0, $J_{3,4e}$ = 2.9 Hz, 1H, C3-H), 5.97 (dd, $J_{2,3}$ = 7.7, $J_{2,4e}$ = 2.0 Hz, 1H, C2-H), 7.32—7.40 (m, 3H, arom).

Optical Resolution of (±)-11-Me-MMPA$^+$I$^-$. The counter anion of the racemic salt was changed from iodide to trifluoroacetate by a treatment with $AgOCOCF_3$ in H_2O, because the iodide salt is less soluble in a solvent for injection. Optical resolution of the chiral salt was performed by a preparative HPLC equipped with an optically active column (Daicel CHIRALCEL OD, 2 cmϕ × 25 cm) at room temperature; eluent C_6H_{14}/EtOH/MeOH/$Et_2NH_2^+CF_3CO_2^-$ = 85/10/5/0.1 (v/v/v/w); flow rate 3 mL min^{-1}; inj. 20 mg/100 μL (EtOH/MeOH = 2/1). The first fraction (retention time 115 min) was the (+)-form and the second (125 min) the (−)-form. Each fraction was concentrated under reduced pressure to give a residue contaminated by $Et_2NH_2^+CF_3CO_2^-$. Isolation of the chiral salt from the residue was accomplished by the following procedure: first, the residue was subjected to a dithionite reduction, second the reduced form obtained was oxidized, and finally the iodide ion was resumed.

To the residue (0.817 g, in which ca. 0.18 g of the chiral salt was contained) dissolved in a buffer (5 mL) were added benzene (5 mL) instead of CH_2Cl_2 and then $Na_2S_2O_4$ (0.17 g, 0.98 mmol) dissolved in a buffer (5 mL); the mixture was then stirred for 1 h under the same conditions as described in the previous part. The organic layer was separated and worked-up, and the obtained residue was purified by the same method as mentioned above to afford 14 mg of chiral 11-Me-MMPAH (yield 7.8%).

Into a 30 mL, round-bottomed flask, chloranil (20.2 mg, 0.082 mmol) was placed. The flask was degassed and filled with argon several times. Dry CH_3CN (15 mL) was added through a syringe, and an argon-purged solution of chiral 11-Me-MMPAH (14 mg, 0.055 mmol) in dry CH_3CN (3 mL) was also added through a syringe. The reaction mixture was stirred for 12 h at room temperature under an argon atmosphere in the dark. The solution turned red. After the solvent was evaporated from the mixture under reduced pressure, a purple residue was obtained.

The residue was treated by an anion-exchangeable resin (iodide form of IRA-400) with column chromatography at room temperature to afford 18.5 mg of chiral 11-Me-MMPA$^+$I$^-$ as a yellow paste: Yield 88%; (+)-11-Me-MMPA$^+$I$^-$: $[\alpha]_D^{25}$ +188° (c = 0.550, MeOH); (−)-11-Me-MMPA$^+$I$^-$: $[\alpha]_D^{25}$ −195° (c = 0.550, MeOH).

CD spectra of (*R*)- (5.35×10^{-5} M) and (*S*)-11-Me-MMPA$^+$I$^-$ (5.44×10^{-5} M) in MeOH were recorded in a 0.1 cm path-length cell at room temperature (Fig. 1).

Reactions. Two types of reduction of 11-Me-MMPA$^+$I$^-$ were studied. The ^{1}H NMR spectra of the products in CD_3CN (Fig. 3) elucidated the *anti* : *syn* stereochemistry of the reactions.

With $Na_2S_2O_4$ in D_2O. The buffer used here was prepared with D_2O instead of H_2O. To the 11-Me-MMPA$^+$I$^-$ (9.8 mg, 0.026 mmol) dissolved in a buffer (2.5 mL) was added CH_2Cl_2 (2.5 mL), and then $Na_2S_2O_4$ (9.1 mg, 0.052 mmol) dissolved in a buffer (2.5 mL); the mixture was then stirred for 5 h. The other reaction conditions and work-up procedures were the same as in the preparation of 11-Me-MMPAH.

With Me_2PNPH-4-*d* in CD_3CN. The reactions of racemic, (+)-, or (−)-11-Me-MMPA$^+$I$^-$ (18 mg, 0.04 mmol) with (4*R*)- or (4*S*)-Me_2PNPH-4-*d* (12 mg, 0.04 mmol) in CD_3CN (700 μL) were run, especially in a NMR tube for 12 h at 23 °C under an argon atmosphere in the dark. After the solvent had been evaporated from the mixture under reduced pressure, the obtained residue was purified by column chromatography on aluminium oxide with CH_2Cl_2 as an eluent.

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