Reduction by a Model of NAD(P)H. 33. Steric and Electronic Effects on Asymmetric Reduction of 2-Acylpyridines

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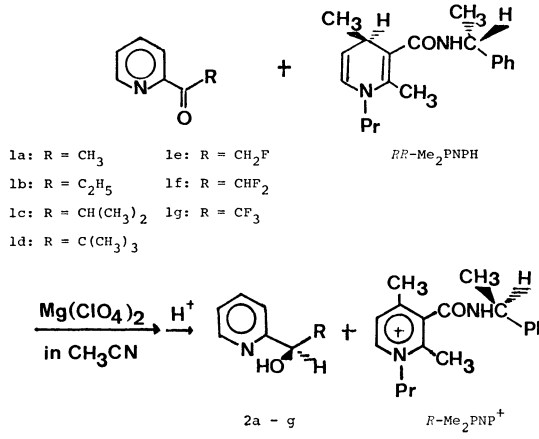
Series of alkyl and fluorinated alkyl 2-pyridinyl ketones have been reduced by a chiral NAD(P)H-model (Me_2PNPH) in the presence of magnesium ion in acetonitrile. Optical yield decreases in the order of substituent: $CH_3 > C_2H_5 > C(CH_3)_3 > CH(CH_3)_2$ and $CH_3 > CH_2F > CHF_2 > CF_3$. The results have been interpreted in terms of conformation of the substrates for alkyl 2-pyridinyl ketones and of electronic competitional effect between two substituents for fluorinated alkyl 2-pyridinyl ketones. Magnesium ion freezes intermolecular arrangement at the transition state of the reduction.

Chiral *N*-(α-methylbenzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH) reduces certain ketones in the presence of magnesium ion in acetonitrile resulting in excellent chemical and optical yields.[1] Conformation of the product from the reaction reveals that the carbonyl-oxygen in a substrate points toward the ring-nitrogen of Me_2PNPH and the polar (electronegative) substituent in the ketone faces against the (electronegative) carbamoyl group of Me_2PNPH.[2] Relative bulk of substituent on the carbonyl group in a substrate seems to have little influence on intermolecular arrangement at the transition state of the reduction. Namely, the pyridinyl moiety behaves as a polar substituent in the reduction of 2-acetylpyridine, whereas trifluoromethyl group is a polar substituent in the reduction of α,α,α-trifluoroacetophenone. The stereospecificity of the reduction is so excellent that it is interesting to obtain further insight into the factor(s) that is operating to determine the stereochemical course of the reduction. Evidence obtained from the study may provide an information on the mechanism of stereochemical transformation.

In this paper, we wish to report results from the reduction of series of 2-acylpyridines and α-fluorinated 2-acylpyridines.

Results

2-Acylpyridines (**1a—d**) and α-fluorinated 2-acylpyridines (**1e—g**) were reduced to the corresponding alcohol by *RR*-Me_2PNPH in the presence of equivalent amount of magnesium perchlorate in dry acetonitrile



at room temperature in the dark. Chemical yields and conversion percentages are listed in Table 1. For the products **2a** and **2b**, enantiomer excess was calculated from their observed optical rotations, whereas those for the other products were calculated from their ^1H- and ^{19}F-NMR spectra by the aid of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA).[3] Absolute configurations of the products were elucidated independently from their signs of optical rotations and CD spectra as well as chemical shifts in NMR spectra of the corresponding MTPA esters. Results are summarized in Table 2.

Complexation constants, *K*, for complexes of 2-acylpyridines and magnesium ion were measured spectrophotometrically,[4] and the results are listed in Table 3.

It has been confirmed that C_4-hydrogen in Me_2PNPH is transferred onto the carbonyl-carbon in a substrate without exchange and that the chirality on the carbamoyl-side chain exerts no influence on the stereochemical course of the reduction in the presence of

Table 1. Chemical yields and conversion percentages from the reduction

Substrate	R in **1**	Yield/%[a]	Conversion/%[b]
1a	CH_3	50.1	100
1b	C_2H_5	45.2	76
1c	$CH(CH_3)_2$	78.3	92
1d	$C(CH_3)_3$	40.3	47
1e	CH_2F	43.3	98
1f	CHF_2	39.4	100
1g	CF_3	35.7	100

a) Isolated yield. b) The amount of consumed substrate.

Table 2. Enantiomer excess and absolute configuration of excess enantiomer

Alcohol	R in **2**	e.e./%	Configuration
2a	CH_3	62.8	*R*
2b	C_2H_5	52.1	*R*
2c	$CH(CH_3)_2$	≈0	—
2d	$C(CH_3)_3$	43.4	*R*
2e	CH_2F	53.5	*S*
2f	CHF_2	30.3	*S*
2g	CF_3	16.5	*S*

Table 3. Complexation constant for complexes of 2-acylpyridines and magnesium ion[a)]

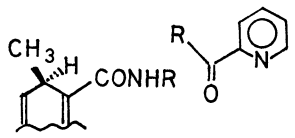
Acylpyridine	R in **1**	K/M^{-1}
1a	CH_3	283
1b	C_2H_5	279
1c	$CH(CH_3)_2$	124
1d	$C(CH_3)_3$	18.6
1e	CH_2F	—[b)]
1f	CHF_2	—[b)]
1g	CF_3	—[b)]

a) In acetonitrile at 25 °C. Estimated error is ±2%.
b) Too small to be observed accurately.

magnesium ion.[1)]

Discussion

α-Fluorinated 2-Acylpyridines. Configurations of alcohols **2a** and **2e—g** reveals that, regardless the number of fluorine atom, the pyridinyl moiety in the ketone faces against carbamoyl group in Me_2PNPH at the transition state of the reduction as depicted by **3**. However, the stereospecificity is largely affected



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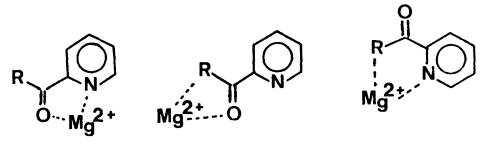
by the number of fluorine-substituent. The result can be accounted for by the difference in electronegativity of substituents on the carbonyl group: as the number of fluorine atom in the substituent R increases, the difference in electron-withdrawing ability between R and pyridinyl group becomes smaller and recognition of polarity-difference becomes difficult. Consequently, magnesium ion can coordinate onto both pyridinyl and fluorinated alkyl groups (See structures **4a—c**).



4a 4b 4c

Note that trifluoromethyl group is the coordination-site in the reduction of α,α,α-trifluoroacetophenone and that complexation constants for **1e**, **1f**, and **1g** are too small to be measured with a reasonable accuracy. The latter evidence indicates that the pyridinyl-nitrogen has no lone-electron pair available for the coordination at least at the ground state of these ketones.

2-Acylpyridines. According to the structure **3**, the substituent R faces against the open-side of Me_2PNPH. Nevertheless, the increase in bulk of R results in the decrease in the stereospecificity of the reduction. The substrate **1c** exerts an abnormal stereospecificity. It is obvious that relative bulk of the substituents cannot account for the result.

Previously we suggested that the change in complexation constant is due to the distortion of dihedral angle between the planes of pyridinyl and acyl groups.[4)] Free 2-acylpyridine in a solution exists with the conformation in which pyridinyl-nitrogen and carbonyl-oxygen sit themselves in the *E*-form.[5)] On the other hand, ^{13}C-NMR, IR, and other spectroscopic studies have revealed that some 2-acylpyridines serve as bidentate ligands that coordinate onto a bivalent metal ion with the nitrogen and oxygen being in the *Z*-form.[6-8)] 2-Acetyl- (**1a**) and 2-propionyl- (**1b**) pyridines are 2-acylpyridines of this kind (Fig. 1a). A large complexation constant suggests that the conformation of the complex is rigid. In these 2-acylpyridines, steric repulsion between the substituent R and pyridinyl-hydrogen on C_3 is negligibly small.

An inspection with a CPK-model, however, suggests that the *t*-butyl group in **1d** is so bulky that the dihedral angle in a stable conformation of complexed **1d** should be about 90° (Fig. 1b). The conformation shown in Fig. 1b′ has extremely high steric strain because of Mg^{2+}–Bu^t repulsion. Small complexation constant for this compound supports the idea that **1d** is no more a bidentate ligand to magnesium ion. Although magnesium ion cannot behave as a fixer

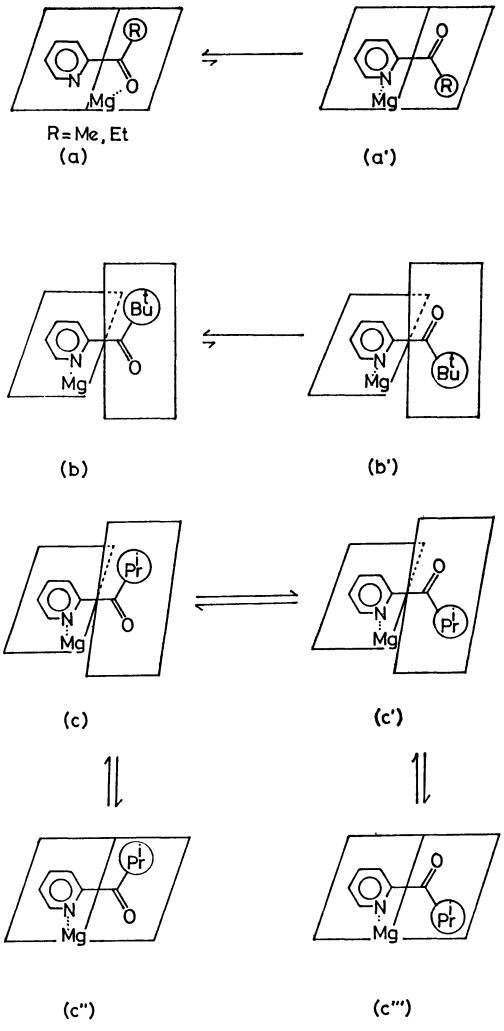


Fig. 1. Conformations of (a) 2-acetyl- and 2-propionylpyridines, (b) 2-pivaloylpyridine, and (c) 2-isobutyrylpyridine in the complex with magnesium ion.

of conformation of **1d**, the steric bulk of *t*-butyl group itself freezes the conformation intrinsically resulting in relatively satisfactory stereospecificity.

The situation is different in **1c**. The steric bulk of 2-propyl group is too large to set two planes coplanar, but it is not large enough to freeze the conformation. Stabilization energy by bidentate coordination onto magnesium ion is not so large as those for **1a** and **1b** but larger than that for **1d**, as seen in the magnitude of complexation constant. Therefore, all four possible rotomers (Fig. 1c) are available as a part of the transition-state complex of the reduction with **1c**, and net result appears non-stereospecific.

Role of Magnesium Ion. The substituent effect on the stereospecificity described above coincide with the idea proposed previously[1,2] that stereospecificity of the reduction is mainly defined by electronic effect. The steric effect has only secondary importance, if any, to define intermolecular arrangement at the transition state of the reduction. However, steric bulk of a substituent in a substrate exerts intrinsic effect on the conformation of the substrate.

Magnesium ion-catalysis for the stereospecificity has an origin in tetradentate sandwich-type coordination to freeze the configuration of transition-state complex (Fig. 2): dihydropyridinyl-nitrogen and carbamoyl-oxygen in Me_2PNPH on one side and pyridinyl-nitrogen or other electronegative substituent and carbonyl-oxygen in a substrate on the other side.[9]

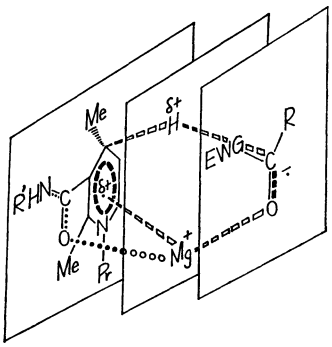


Fig. 2. Schematic illustration of the transition state of the reduction.

Experimental

Instruments. UV, IR, NMR, and mass spectra were recorded on Union Giken SM-401, Hitachi EPI-S2, JEOL JNMFX-100, and JEOL JMSO-1SG or Hewlett Packard 5992B GC/MS spectrometers, respectively. The optical activity was measured on a Perkin-Elmer 241 polarimeter. The CD spectra were obtained with a JASCO J-20 spectropolarimeter. A Yanaco G-1800F and Varian Aerograph Model 920 were used for VPC, and a Yanaco Model L-2000 was used for high-pressure liquid chromatography. Melting and boiling points were not corrected.

Materials. Acetonitrile was distilled three times over phosphorus pentaoxide and stored over 4A molecular sieves under an atmosphere of argon. Anhydrous magnesium perchlorate was dried at 100 °C and stored in a vacuum desiccator over phosphorus pentaoxide. 2-Acetylpyridine (**1a**) (bp 95 °C/34 mmHg) was purchased from Nakarai Chem. Co.

2-Propionylpyridine (**1b**) (bp 96.5—97.5 °C/20 mmHg),

Table 4. Optical rotations of product alcohols

Alcohol	$[\alpha]_D$	*c*	Temp/°C	Solvent
2a	+35.6	1.03	25	EtOH
	+26.8	1.95	25	CCl_4
2b	+38.0	1.68	25	EtOH
	+23.8	1.59	25	CCl_4
2c	+0.390	0.770	25	EtOH
	+0.232	0.818	25	CCl_4
2d	+27.0	0.215	20	EtOH
	+12.8	1.67	25	CCl_4
2e	+36.9	0.255	20	MeOH
	−3.04	1.19	20	CCl_4
2f	+6.21	0.145	20	MeOH
	−10.3	0.800	20	CCl_4
2g	+10.2	0.420	20	MeOH
	−0.821	0.875	20	CCl_4

Table 5. ^{1}H- and ^{19}F-NMR chemical shifts of (+)-MTPA esters of the product alcohols

Alcohol	Config. of alcohol	^{1}H Chemical shift[a]			^{19}F Chemical shift[b]	
		Acid-OMe	Alcohol-H	Alcohol-R	Acid-CF_3	Alcohol-R
2a	*R*	—	—	—	72.01	—
	S	—	—	—	72.01	—
2b	*R*	—	—	—	71.87	—
	S	—	—	—	71.87	—
2c	*R*	3.49	5.82	0.88	71.71	—
	S	3.55	5.82	0.88	71.79	—
2d	*R*	3.52	5.76	0.92	71.45	—
	S	3.52	5.71	0.97	71.56	—
2e	*R*	3.64	6.36	4.82	71.97	154.89
	S	3.53	6.36	4.82	72.29	156.31
2f	*R*	3.55	6.29	6.30	72.16	129.41
	S	3.55	6.25	6.30	72.48	129.16
2g	*R*	3.61	6.40	—	72.18	75.32
	S	3.50	6.43	—	72.36	75.47

a) δ from TMS in $CDCl_3$. b) δ from CCl_3F in $CDCl_3$.

2-isobutyrylpyridine (**1c**) (bp 99.0—100.0 °C/19 mmHg), and 2-pivaloylpyridine (**1d**) (bp 100.5—101.5 °C/20 mmHg) were prepared from the corresponding alkyl cyanides and 2-pyridinyllithium.[10] 2-(Fluoroacetyl)pyridine (**1e**) (mp 70.0—71.0 °C), 2-(difluoroacetyl)pyridine (**1f**) (purified on a silica-gel column), 2-(trifluoroacetyl)pyridine (**1g**) (mp 84.0—85.0 °C) were synthesized from the corresponding esters and 2-pyridinyllithium.[11] Elemental analyses and spectral data were satisfactory for all materials. Racemic alcohols as authentic samples of the products were obtained by reducing the corresponding ketones with sodium borohydride.[12]

General Procedure for the Reduction. One millimole each of *RR*-Me_2PNPH and magnesium perchlorate were dissolved in 25 ml of anhydrous acetonitrile in a sealed flask. One millimole of the substrate in 5 ml of anhydrous acetonitrile was added by injection by using a syringe, and the mixture was allowed to react at room temperature (about 25 °C) for an appropriate reaction time in the dark in an argon atmosphere. The reaction was stopped by the addition of water, and the product was extracted three times with dichloromethane. The combined dichloromethane solution was dried over sodium sulfate. After evaporation of the solvent at below 30 °C under reduced pressure, the residue was chromatographed on a column of silica gel. The product was further purified by preparative VPC or high-pressure liquid chromatography when neccesary. The purity of the product was confirmed by VPC and by elemental analyses. Columns used for VPC were mainly Silicone DC 200 5% (1 m) and DEGS 10% (1 m). Appropriate mixtures of benzene–ethyl acetate or benzene–ether were employed as the eluents for column chromatography. Thus obtained products were subjected for the measurement of optical rotations or converted into the corresponding MTPA esters for NMR spectroscopy. Optical rotations of the products and NMR chemical shifts of the corresponding esters are summarized in Tables 4 and 5, respectively.

Correlation of Physical Units. Physical units used in this report are correlated with SI-units by the following relationship.

1 M=1 mol dm^{-3}, $t/°C = T/K - 273.15$, p mmHg=13.5951 $\times 980.665 \times 10^{-2}$ p Pa.

References

1) A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, *J. Am. Chem. Soc.*, **101**, 7036 (1979).

2) A. Ohno, T. Goto, J. Nakai, and S. Oka, *Bull. Chem. Soc. Jpn.*, **54**, 3478 (1981).

3) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

4) A. Ohno, S. Yasui, and S. Oka, *Bull. Chem. Soc. Jpn.*, **53**, 2651 (1980).

5) J. Barassin, G. Queguiner, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, **1967**, 4707.

6) R. R. Osborne and W. R. McWhinnie, *J. Chem. Soc., A*, **1967**, 2075.

7) Y. Kidani, M. Noji, and H. Koike, *Bull. Chem. Soc. Jpn.*, **48**, 239 (1975).

8) R. A. Gase and U. K. Pandit, *J. Am. Chem. Soc.*, **101**, 7059 (1979).

9) *Cf.* also, A. Ohno, T. Kimura, H. Yamamoto, S. G. Kim, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Jpn.*, **50**, 1535 (1977).

10) J. P. Wibaut, A. P. de Jonge, H. G. P. van der Voort, and P. Ph. H. L. Otto, *Recl. Trav. Chim. Pays-Bas*, **70**, 1054 (1951).

11) T. F. McGrath and R. Levine, *J. Am. Chem. Soc.*, **77**, 3656 (1955).

12) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).