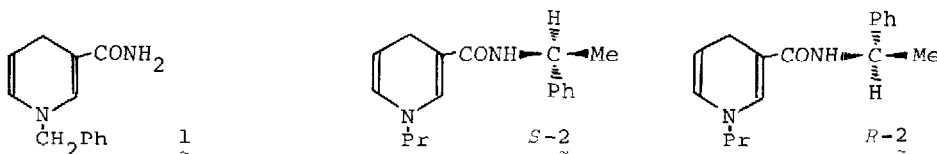


REDUCTION BY A MODEL OF NAD(P)H. X. ASYMMETRIC REDUCTIONS OF
CARBONYL COMPOUNDS IN THE PRESENCE OF MAGNESIUM PERCHLORATE

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Recently, we demonstrated the first example of stereospecific biomimetic oxidation-reductions with models of NAD(P)H.¹⁾ It has also been reported that asymmetric induction is achieved only in the presence of metal ions.^{2,3)} We now wish to report that, with our biomimetic system, the optical purity of the product depends absolutely on the molar ratio of the metal ion to the coenzyme model.



1-Benzyl-1,4-dihydropyridinamide, 1, (1.21 mmol) in dry acetonitrile containing magnesium perchlorate (1.21 mmol) reduced 2-acetylpyridine (1.21 mmol) into 1-(2'-pyridyl)ethanol, 3, in a 63% yield (isolation) after 44 hr under anaerobic condition in the dark at 50°C. The starting ketone was recovered in a 20% yield. On the other hand, the alcohol could not be detected in the reaction mixture without the magnesium salt. Evidence for the direct hydrogen transfer comes from a tracer experiment: when 1-4-d₁ was utilized, the deuterium was introduced into the carbonyl carbon of the substrate with the apparent primary isotope effect of ca. 2.6.⁴⁾ 2-Benzoylpyridine and 2-acetylbenzimidazole were also reduced to the corresponding

alcohols in 70 and 43% yields (vs conversion), respectively, under the same condition, whereas 3- and 4-acetylpyridines, 2-acetyl derivatives of 1-methylpyrrole and thiophene, and 2-pyridylacetone were not reduced.

Reduction of 2-acetylpyridine with (*R*)-(-)-*N*- α -methylbenzyl-1-*n*-propyl-1,4-dihyronicotinamide, *R*-2, in the presence of equimolar amount of magnesium perchlorate afforded optically active (+)-3 in 72% chemical yield, $[\alpha]_D^{24} +14.3^\circ$ (c 1.8, EtOH), which was composed of 25% excess of the (*S*)-(+)-isomer.⁵⁾ On the other hand, the *S*-configurational isomer, *S*-2, reduced the ketone giving (+)-3 predominantly. The reduction of the alcohol was accomplished in the following manner. To the mixture reacted for 44 hr was added small amounts of water and silica-gel (100-200 mesh) and the mixture was evacuated to remove the solvent and water at temperatures below 30°C. The residual silica-gel coated by organic materials was chromatographed on silica-gel with a mixture of benzene and ethyl ether (7:3 v/v) as an eluant. Optical activity was measured after the alcohol isolated in this way was once distilled. The structure was confirmed with tlc, nmr, and elemental analyses.

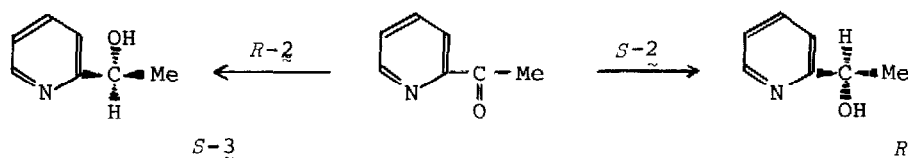
Table 1. Asymmetric Reductions of 2-Acetylpyridine by Optically Active *N*- α -Methylbenzyl-1-*n*-propyl-1,4-dihyronicotinamides.^{a)}

Model Compound, mmol	Mg(ClO ₄) ₂ , mmol	[Metal Salt] (mmol Model Compound)	1-(2'-pyridyl)ethanol			
			Yield, %	$[\alpha]_D^c$	Optical Yield, % ^{c)}	
<i>R</i> -2	2.03	1.01	0.5	66	+22.2°	39
"	0.99	0.52	0.5	48	+20.2°	36
"	1.48	0.92	0.6	68	+20.2°	36
"	1.45	0.98	0.7	55	+20.0°	35
"	1.00	1.00	1.0	72	+14.3°	25
"	1.51	1.85	1.3	82	+13.3°	24
"	1.00	1.56	1.7	58	+10.3°	18
<i>S</i> -2	1.53	1.95	1.3	65	-11.6°	21

a) Reactions were run with 1 mmol of the ketone in acetonitrile for 44 hr at 50°C in the dark.

b) $[\alpha]_D^{24} +56.6^\circ$ was taken as the rotation of pure (*R*)-(-)-or (*S*)-(+)-1-(2'-pyridyl)ethanol: see ref. 5.

c) In 99.5% ethanol at 24°C.



From the result shown in Table 1, it is apparent that the optical yield decreases with increase of the molar ratio of the magnesium salt to the model compound, but it is independent of the concentration of the magnesium salt.

2-Benzoylpyridine behaved similarly.

In the metal-catalyzed reduction of ethyl benzoylformate with the optically active model compounds, the magnitude of asymmetric induction also changes with the change of the molar ratio. However, the mode of dependency differs from that in the reduction of 2-acetylpyridine. Namely, the optical yield increases with the increase of the molar ratio with an asymptote of about 20% (Table 2). In this case again, the concentration of the magnesium salt does not affect the optical yield.

Table 2. Asymmetric Reduction of Ethyl Benzoylformate by Optically Active *N*- α -Methylbenzyl-1-*n*-propyl-1,4-dihydropyridinamide.^{a)}

Model Compound,	Mg(ClO ₄) ₂ , mmol	[Metal Salt] [Model Compound]	Ethyl Mandelate Isolated			
			Yield, %	[α] _D ^{b)}	Optical Yield, % ^{c)}	
<i>R</i> -2	1.00	0.26	0.3	86	-6.9°	6.6
"	1.02	0.52	0.5	82	-8.9°	8.6
"	2.05	1.05	0.5	95	-10.3°	9.9
"	0.99	1.04	1.1	94	-20.4°	19.6
"	0.98	1.99	2.0	95	-18.9°	18.1
<i>S</i> -2	1.14	0.96	0.8	96	+19.3°	18.6

a) Reactions were run with 1 mmol of the keto ester in acetonitrile for 44 hr at room temperature in the dark.

b) In 99.5% ethanol at 24°C.

c) [α]_D + 104° was taken as the rotation of pure ethyl (*R*)-(-)- or (*S*)-(+)-mandelate: see ref. 1.

Since we do not have evidence to propose the role of magnesium ion, it is difficult to explain the present result. One thing which is clearly suggested by the result is that the magnesium ion plays a role to arrange molecules of a substrate and the model compound at the transition state of the reaction. It is also obvious that the effects of magnesium ion on the acceleration of the reaction and on the induction of chirality must be considered separately. Detailed mechanism is under investigation.

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- 4) This value was obtained on the basis of the fact that $\underline{1-4-d_1}$ (100% D-content) gives $\underline{3-d_1}$ with 28% D-content measured on nmr spectrometer: see D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.*, 72, 2261 (1955).
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