-phenylpropenal (PPA) (Chung and Park, 1982). These substrates did not afford the rearranged products indicating that there is no radical intermediacy in the reaction. A similar result was obtained in the HLADH oxidation of α-hydroxyalkylcyclopropanes (MacInnes et al. 1982). It is known that the cyclopropylmethyl free radical isomerizes into the butenyl free radical quantitatively (van Niel and Pandit, 1983), but the whole product from the enzymatic reduction reserved the cyclopropyl moiety.

5 ASYMMETRIC REDUCTION BY MODEL COMPOUNDS OF NAD(P)H

5.1 Model Reactions of NAD(P)H Dependent Dehydrogenases

Within a molecule of NAD(P)H, the 1,4-dihydronicotinamide moiety acts as a reducing reagent. Thus, a 1,4-dihydropyridine derivative where the ring nitrogen is substituted by a simple substituent, such as 1-propyl-1,4-dihydronicotinamide (PNAH), 1-benzyl-1,4-dihydronicotinamide (BNAH), or Hantzsch ester (HEH), can be considered as a model compound for NAD(P)H.

\[
\text{NAD(P)H} \quad \text{NAD(P)H} \quad \text{NAD(P)H}
\]

PNAH \quad BNAH \quad HEH

Simulation of the reactions of dehydrogenases using 1,4-dihydropyridine derivatives has been widely investigated (Eisner and Kuthan 1972, Stout and Meyers 1982). These compounds reduce C=O, C=C, C=N, and C=S double bonds as well as flavin and metal ions (Kil1 and Widdowson 1978, Okamoto et al. 1979). However, they are not so reactive toward the reduction compared with NAD(P)H in a biological system where an apoenzyme participates as a catalyst. The 1,4-dihydropyridine derivatives in a nonenzymatic system can reduce only those substrates like α,α,α-trifluoroacetophenone (TFA), hexachloroacetone (HCA), and maleic anhydride (MA). That is, the substrate should be strongly electron-deficient in order to be reduced.

\[
\text{TFA} \quad \text{HCA} \quad \text{MA}
\]
Considering that the reactivity of the 1,4-dihydropyridine moiety extracted from the dehydrogenase system is very low, it is easily noticed that a specific field created by amino acid residues from the apoenzyme is very important for acceleration of the reaction. At the same time, it should be noted that such a reaction field at the active site of the enzyme contributes to the stereospecificity of the reaction. Although NAD(P)H contains chiral centers within the molecule, these chiralities exert no effect on asymmetric reduction of a substrate. Induction of the chirality in an enzymatic system depends on the chiral environment arranged by the apoenzyme. Thus, it is necessary to introduce a chiral environment around the 1,4-dihydropyridine ring of NAD(P)H model compounds to simulate the asymmetric reduction by dehydrogenases.

5.2 The First Asymmetric Reduction

The first example of the asymmetric reduction by an NAD(P)H model compound was reported in 1975 (Ohnishi et al. 1975a). By means of

Scheme 9

![Scheme 9](image)

\[ R-PNPH : R = \pi\text{-propyl} \quad EBF \]
\[ R-BNPH : R = \text{benzyl} \]
\[ R-\text{Cl}_2\text{BNPH} : R = 2,6\text{-dichlorobenzyl} \]

<table>
<thead>
<tr>
<th>Reducing reagent</th>
<th>Configuration of the product</th>
<th>e.e. [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R-PNP^+ )</td>
<td>( R = \pi\text{-propyl} )</td>
<td>S-EM</td>
</tr>
<tr>
<td>( R-BNP^+ )</td>
<td>( R = \text{benzyl} )</td>
<td>R-EM</td>
</tr>
<tr>
<td>( R-\text{Cl}_2\text{BNP}^+ )</td>
<td>( R = 2,6\text{-dichlorobenzyl} )</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Asymmetric reductions of ethyl benzoylformate with chiral model compounds.