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REDUCTION BY A MODEL OF NAD(P)H. XX. DEPENDENCE OF ENANTIOSPECIFICITY ON THE CONVERSION OF REACTION

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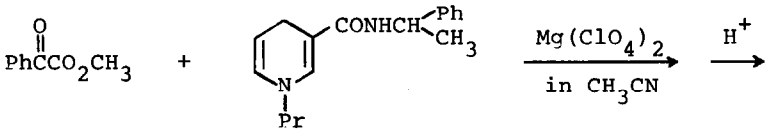
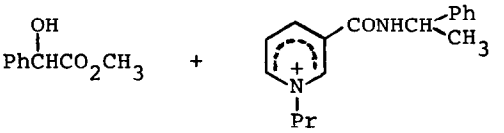
Stereochemistry[1] and mechanism[2] of the asymmetric reduction of methyl benzoylformate(1) by optically active N-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide(PPNAH)[3] have been reported. It was also reported that the



1 PPNAH



2 $PPNA^+$

enantiospecificity of the reduction depends absolutely on the molar ratio of the metal ion to the coenzyme model.[4]

This communication describes that the optical purity of the product, methyl mandelate(2), depends not only on the molar ratio of the metal ion to the coenzyme but also on the percentage of the conversion of the reaction and that the configuration of 2 isolated at an early stage of the reaction is opposite to that of 2 isolated after the reaction was complete. Although the changes in enantio-

specificity with the change in solvent,[5] temperature,[6] or aging time[7] are known for some cases, this is the first report, to the best of our knowledge, which describes the dependence of enantiospecificity on the conversion of reaction.[8]

For most runs, a solution of 1 mmol of magnesium perchlorate in 4 ml of acetonitrile was added to 6 ml of an acetonitrile solution containing 1 mmol of *R*- or *S*-PPNAH and 1 each. Both solutions were kept at -3°C under argon atmosphere in the dark for 30 min before mixing. In some runs, the order of the addition of reagents was altered. The reaction was stopped by pouring the reaction mixture into 100 ml of water and the organic materials were extracted with four portions of 100 ml each of methylene chloride. The extract was concentrated *in vacuo* at temperatures below 30°C. The percentage of the conversion of reaction was calculated by analyzing the amount of 1 on glc (5% PEG, 1 m, 170°C). The concentrated extract was chromatographed on a column of silica gel with benzene-ethyl acetate (85:15, v/v) as an eluent. Fractions that contained 2 were collected and concentrated *in vacuo* at temperatures below 30°C to give 2 as white solid (mp 53°C). After the purity was confirmed by glc, nmr, and elemental analyses, the optical activity of 2 was measured on a Perkin-Elmer 241 Polarimeter.

Figure 1 shows the dependence of the optical yield of 2 (expressed in enantiomer excess[9]) on the percentage of the conversion of the reaction. The yield is independent of the order of the addition of the reagents, of the reaction temperature, and of concentrations of substrates. Since it is known that NADH and its analogs form charge-transfer complexes with their oxidized forms[10] and since $PPNA^+$ is accumulated as the reduction proceeds, the effect of $PPNA^+$-salt on the optical yield was tested. The result is also shown in Figure 1. When *S*-$PPNA^+ClO_4^-$ was added to the *R*-PPNAH system the optical yield of 2 decreased remarkablly: racemic 2 was obtained when a solution of *R*-PPNAH containing an equivalent amount of *S*-$PPNA^+ClO_4^-$ was kept for 9 hr at a room temperature prior to the reaction. The observation indicates that there is significant interaction between PPNAH and a $PPNA^+$-salt. It is known that PPNAH transfers a (net) hydride to the 4- and 6-positions of $PPNA^+$.[11] However, it was established that the 1,6-dihydro-isomer of PPNAH has no ability for the reduction.

Although the result obtained from the reaction in the presence of equivalent

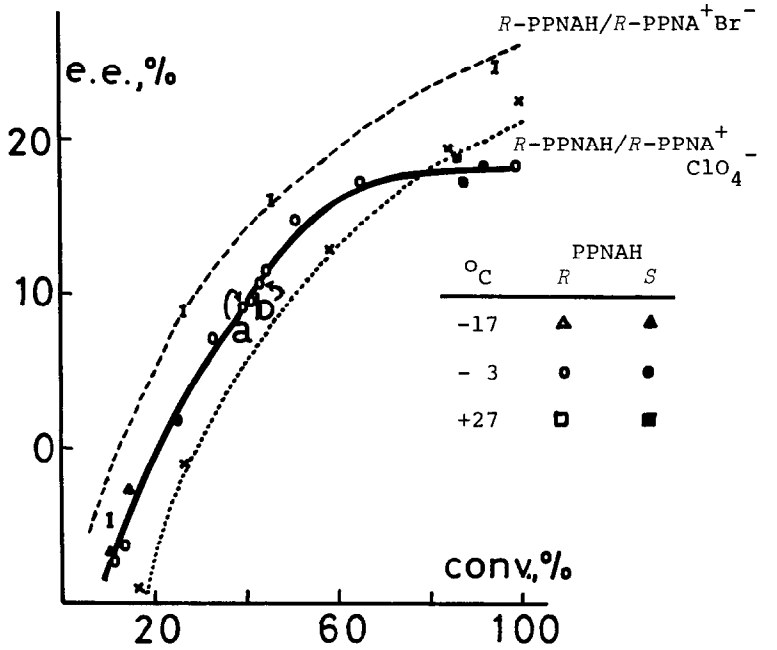


Figure 1. Dependence of enantiomer excess on the conversion of the reaction. a; PPNAH was added to a mixture of 1 and Mg^{++}. b; 1 was added to a mixture of PPNAH and Mg^{++}. All reagents were used in equivalent molar amounts.

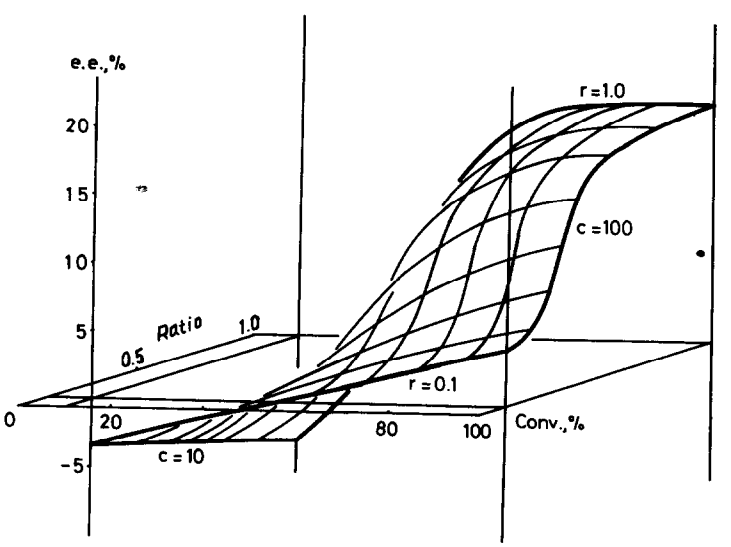


Figure 2. The surface of the enantiomer excess.

amount of a $PPNA^+$-salt indicates that the salt affects the optical purity of 2, the effect seems to be too small to account for a large variation in the enantiomer excess (>25%) observed during the course of the reaction. It should be noted, however, that enantiospecificity has no asymptote in the presence of the salt and the counter anion of the salt also affects the specificity.

Another chiral source which is accumulated in the reaction mixture as the reduction proceeds is the anion of 2. Unfortunately, we have no results to discuss on the effect of this species and the research is in progress toward this end.

Figure 2 represents two-dimensional correlation of the enantiomer excess on the conversion of the reaction and on the $[Mg(ClO_4)_2]$/[PPNAH] molar ratio.

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