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REDUCTION BY A MODEL OF NAD(P)H. CONTRIBUTION OF METAL ION TO ASYMMETRIC REDUCTION OF TRIFLUOROACETOPHENONE

Yutaka OHNISHI*, Takashi NUMAKUNAI
Sagami Chemical Research Center
Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan
Atsuyoshi OHNO
Institute for Chemical Research
Kyoto University, Uji-shi, Kyoto 611, Japan

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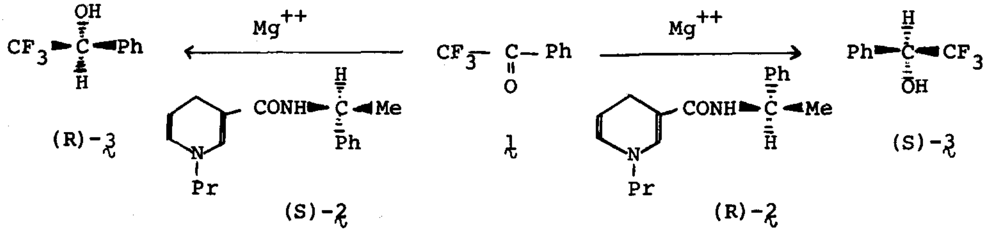
In spite of tremendous works on mimetic reactions of NAD(P)H-dependent dehydrogenases,[1] stereochemical problem has not been paid much attention. Recently, we reported that optically active 1,4-dihydronicotinamide derivatives, in which the chiral center is separated from the reaction center by five atoms, results in asymmetric reduction of α-keto esters by the aid of magnesium or zinc perchlorate.[2] We wish now to present the stereochemical results from the reaction of α,α,α-trifluoroacetophenone (**1**)[3] with optically active N-α-methylbenzyl-1-n-propyl-1,4-dihydronicotinamide (**2**) and to show the essential role of the magnesium ion for the asymmetric reduction.

A solution of **1** (0.60g, 3.45 mmol) and (R)-(-)-**2**, $[\alpha]_D^{24}$ -169° (c 3.0, MeCN), (1.62g, 6.00 mmol) in dry acetonitrile (30 ml) was allowed to stand at room temperature for 6 days in the dark under anaerobic condition. The resulting solution was quenched with water (5 ml). The mixture was concentrated <u>in vacuo</u> and the residue was carefully column chromatographed on silica gel with benzene as an eluant. Phenyl trifluoromethyl carbinol (**3**) obtained in 30% yield was optically inactive. On the other hand, the same reduction in the presence of magnesium perchlorate (1.50g, 6.73 mmol) gave the optically active alcohol (S)-**3** in 58% yield, $[\alpha]_D^{24}$ +5.8° (c 1.5, EtOH), with the optical purity of ca. 16%.[4] When (S)-(+)-**2**, $[\alpha]_D^{25}$ +169° (c 2.0, MeCN), was subjected to the asymmetric reduction of **1**, the alcohol **3** with the R-configuration, $[\alpha]_D^{25}$ -6.9° (c 0.9, EtOH), was obtained predominantly.

It was found that the magnesium ion not only induces asymmetric reduction but also accerelates the reaction: the yield of **3** in the reduction with 1-benzyl-1,4-dihydronicotinamide without magnesium perchlorate was only 3% after a day at 30°C, whereas it was 20% in the presence of magnesium ion. There are several examples, in which mimetic reaction is accerelated by a metal ion.[2,5,6]



Alcohol dehydrogenases require zinc ion as a cofactor and, recently, it was proved that, in the reaction of liver alcohol dehydrogenase, zinc ion behaves as a Lewis acid to coordinate with the carbonyl-oxygen of a substrate and thereby reduce the electron density at the carbonyl-carbon.[7] However, there is no discussion on the role of ametal ion for the stereospecificity and stereoselectivity of biological and biomimetic hydrogen-transfer processes. The present result seems to suggest a possibility that a metal ion contributes to asymmetric induction as well as electronic distribution also in enzymatic reactions.[8]

Although it is difficult to rationalize the origin of the activity of magnesium ion in the present system, we would like to propose two possibilities. The one is that in which magnesium ion coordinates with the dihydronicotinamide fixing its conformation in such a way as to induce the chirality at the C-4 position and, at the same time, enhancing its reactivity.[2] The other is based on the idea that magnesium ion coordinates with both the substrate and the substituted dihydropyridine. The coordination makes the non-covalent intermediate,[3] or the radical-ion pair[9] so tight that the chirality in the coenzyme model affects the stereochemistry of the reaction more effectively than in the reaction without magnesium ion.

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