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ROLE OF HYDROXYL GROUPS IN THE STEREOCHEMISTRY OF HYDROGEN TRANSFER FROM CHIRAL NAD(P)H MODEL TO CARBONYL

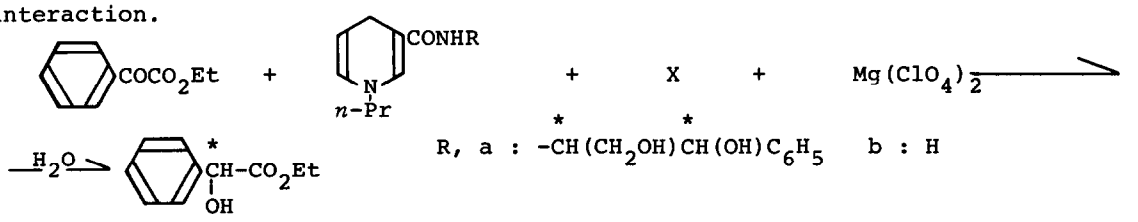
Taketoshi MAKINO, Tetsuji NUNOZAWA, Naomichi BABA,
Jun'ichi ODA and Yuzo INOUYE*
Institute for Chemical Research, Kyoto University, Uji,
Kyoto 611, Japan

Summary: Asymmetric reduction of α-ketoester with a chiral dihydronicotinamide was significantly affected by chiral aromatic additives, capable of exerting an attractive interaction with dihydropyridine ring, which was further consolidated through the chelation of hydroxyl groups with magnesium.

In spite of the extensive works on biomimetic reactions of NAD(P)H-dependent dehydrogenases,[1] stereochemical problem remains as yet open. Some attention has, however, been directed to this aspect from the viewpoint of asymmetric NAD(P)H model reactions.[2]

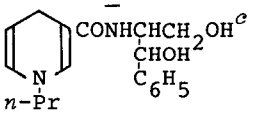
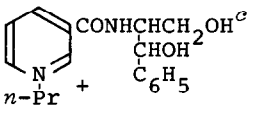
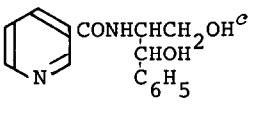
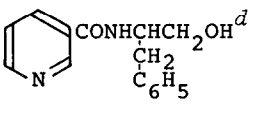
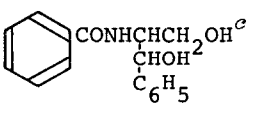
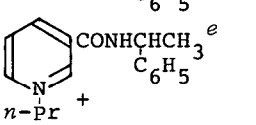
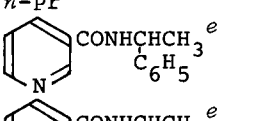
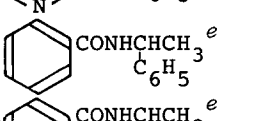
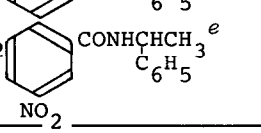
In a concurrent paper,[3] we have discussed in detail the important participation of the oxidised NAD species[4] in the stereochemical course of the magnesium perchlorate-mediated asymmetric reduction of α-ketoester with special emphasis on the hydroxyl functions in the chiral model compound.

We wish, at this time, to present additional evidence for the deduction[3]: present experimental findings show that an interaction between the reduced dihydropyridine- and the oxidised pyridine-derivatives furnishes new chiral environment, potential for induction of chirality in the reduction product, and that hydroxyl groups in the present model systems are significantly conducive to the interaction.



Typically, a solution of ethyl benzoylformate (178.2 mg; 1.0 mmole), *N*-2'-

Table. Stereochemical Results of Asymmetric NAD(P)H Model Reaction Under the Effect of Additional Chiral Substances

run	R	X[a]	reaction yield %	optical yield[b] %	$[\alpha]_D^{25}$ (in $CHCl_3$)	Config.
1	a	–	69	26.3	+33.16	(*S*)
2	a		31	2.9	+ 3.72	(*S*)
3	a		54	51.5	+64.98	(*S*)
4	b		61	28.0	+35.37	(*S*)
5	a		59	47.3	+59.70	(*S*)
6	b		68	12.4	+15.65	(*S*)
7	a		61	19.6	+24.71	(*S*)
8	b		67	4.8	+ 6.10	(*S*)
9	a		52	34.2	+43.10	(*S*)
10	b		66	5.3	+ 6.70	(*S*)
11	a	Me_2NCHCH_2OH[c] $CHOH$ C_6H_5	30	12.0	+15.18	(*S*)
12	b		44	24.7	+31.20	(*S*)
13	b		81	1.2	+ 1.47	(*S*)
14	b		79	0.3	+ 0.45	(*S*)
15	b		57	2.3	+ 2.94	(*S*)
16	b		69	0.9	+ 1.11	(*S*)

[a] All supplementary compounds used showed wholly satisfactory purities on elementary analyses, pmr and ir spectra. [b] Based on the reported maximum rotation of (*S*)-(+)-, (*R*)-(-)-ethyl mandelate, ± 126.2° in chloroform.[5] [c] Prepared from optically active amine, (4*S*, 5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane, generously supplied from Boehringer GmbH Mannheim Co. [d] Prepared from L-phenyl alanine. [e] Prepared from optically active α-methyl benzylamine, $[\alpha]_D$ -39.4°, in 98.2 % optical purity.

(1'-phenyl-propane-1',3'-diol)-N_1-*n*-propyl-1,4-dihydronicotinamide[6] (316.4 mg; 1.0 mmole), *N*-2'-(1'-phenyl-propane-1',3'-diol)-nicotinamide (272.3 mg; 1.0 mmole) and magnesium perchlorate[7] (111.6 mg; 0.5 mmole) in dry acetonitirile (10 ml) was stirred at room temperature under N_2 in the dark for 22 hr, after which was quenched (1 ml of water). The product mandelate was extracted with dichloromethane and purified by t.l.c., $[\alpha]_D^{25}$ 59.70° (*c* 1.005, chloroform), 47.3 %e.e. The integrity of the mandelate was confirmed by v.p.c., and elementary analysis; yield, 102 mg (57 %), (run 5).

As can be seen from the tabulated data, the addition of pyridine-derivative (run 5, 47.3 %e.e.) or its iodide salt (run 3, 51.5 %e.e.) caused a dramatic increase in optical yield of the mandelate. This finding not only asserts the previously deduced participation[3] of the $NAD(P)^+$ analogue in the transition state complex and cogently suggests an attractive interaction between the additive X and 1,4-dihydronicotinamide nucleus in the present system, but also is in agreement with the reported interaction[4] of the same kind. Such was found to be the case also in run 9, in which aromatic nucleus of the additive X is capable of exerting an attractive interaction with 1,4-dihydropyridine. It is reasonable to assume that the attractive interaction is further consolidated by the chelation with magnesium through hydroxyl handles in the side chain of these two species. The reduced enantiomeric excess down to 19.6 %e.e. (run 7), where additive X contains only one hydroxyl function available for chelation, stands for this view. It then seems likely that one face of the dihydropyridine ring is specifically blocked by the proximity of pyridinium-, pyridine- or phenyl-rings of the additives in runs 3 - 6, 9 and 10. Extent of the blockade and stability of the chelation were actually reflected in the stereochemical outcome (*vide supra*). The stereochemical effect of the chiral additives seems to be most exquisitely felt in the product carbinol when these two interacting species are ensembled together through the chelation with one magnesium atom shared by totally four hydroxyl functions of both participants to form the transition state complex.

Results obtained in runs 4, 6 and 10, where available hydroxyl functions

are missing in the 1,4-dihydropyridine, are along this line and suggest an insufficient and therefore less specific blockage of dihydropyridine face by the supplementary X. In accord with expectation, inferior enantiomeric enrichment was found for runs 13[8] - 16 with the additives lacking polar functions and therefore poor at coordination with magnesium.

It may be safely concluded that hydroxyl groups in the present system play an important role in discrimination between enantiotopic faces of the prochiral substrate carbonyl by one of the two diastereotopic hydrogens at C-4 of dihydropyridine ring, and this constitutes another example in which electrostatic factors are very important for higher asymmetric yields to be attained.

References and Notes

1. R.J.Kill and D.A.Widdowson,'Bioorganic Chemistry vol. IV', ed. E.E.van Tamelen, Academic Press, London, 1978, p.239, and references cited therein.
2. (a) Y.Ohnishi, M.Kagami, and A.Ohno, *J. Amer. Chem. Soc.*, 97, 4766 (1975). (b) K.Nishiyama, N.Baba, J.Oda, and Y.Inouye, *Chem. Comm.*, 101 (1976). (c) T.Makino, N.Baba, J.Oda, and Y.Inouye, *Chem. and Ind.*, 277 (1977). (d) A.Ohno, M.Ikeguchi, T.Kimura, and S.Oka, *Chem. Comm.*, 328 (1978). (e) H.J.van Ramesdonk, J.W.Verhoeven, U.K.Pandit, and Th.J.de Boer, *Rec. Trav. Chim.*, 97, 195 (1978).
3. T.Makino, T.Nunozawa, N.Baba, J.Oda, and Y.Inouye, *J. Chem. Soc.*, submitted for publication.
4. (a) J.Ludowieg and A.Levy, *Biochemistry*, 3, 373 (1964). (b) H.Minato, T.Ito, and M.Kobayashi, *Chem. Letts.*, 13 (1977). (c) P.van Eikeren and D.L.Grier, *J. Amer. Chem. Soc.*, 99, 8057 (1977).
5. R.Roger, *J. Chem. Soc.*, 2168 (1932).
6. The preparation of this compound is described elsewhere.[3]
7. 0.5 molar amount of magnesium perchlorate was used according to the optimization in the preceding work.[3]
8. The observed asymmetric induction may possibly be attributed to a conceivable competitive side path which involves an initial formation of a chiral reductant resulting from the reduction of the added nicotinium salt by achiral *n*-propyldihydronicotinamide used,[4b,c] followed by the reduction of substrate carbonyl with the intermediate chiral NAD(P)H model to give the end product carbinol. Should the rate of the side path be faster than that of the reduction of substrate by achiral *n*-propyldihydronicotinamide in association with the added nicotinium salt, the same extent of e.e.(9.9 %) as reported by Ohnishi[9] in the same reaction could necessarily be expected for the present system as well. This was actually not the case, so that such a side path, if any, is negligible in run 4 as well as run 13.
9. Y.Ohnishi, T.Numakunai, T.Kimura, and A.Ohno, *Tetrahedron Letts.*, 2699 (1976).

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