## NAD(P)<sup>+</sup>-NAD(P)H MODEL. 38. REDUCTION OF ALDEHYDE BY 1,4-DIHYDROQUINOLINE DERIVATIVE

Atsuyoshi OHNO\*, Yuji ISHIHARA, Satoshi USHIDA and Shinzaburo OKA Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611 JAPAN

Summary: Benzaldehyde are reduced to benzyl alcohol by a model compound of NAD(P)H almost quantitatively. Reductions of some other aldehydes are also mentioned.

Biomimetic reduction of carbonyl compounds by NAD(P)H-models has been a subject of wide interest. Substrates that can be reduced in model reactions, however, are limited to those that are activated by some means. Activation has been done by substituting an electron-withdrawing group on the carbonyl-carbon(1) or by using electrophilic catalyses(2). A 1,4-dihydropyridine derivative as a model of NAD(P)H is quite susceptible toward the attack by an electrophile and this sort of compounds cannot be used in acidic media or with a strong Lewis acid such as aluminum chloride.

Shinkai and his co-workers have developed a model of new type which is stable toward electrophilic attack(3) and succeeded in reducing a non-activated carbonyl compound, benzaldehyde, in at most 30% yield under hydronium ioncatalysis(4). Unfortunately, their model compound, a 1,4-dihydroquinoline derivative, is known to be less reactive than the corresponding 1,4-dihydropyridine derivative. Substitution of alkyl groups on the 1,4-dihydropyridinering as well as on the carbamoyl group, on the other hand, activates the reactivity of the model compound(5). Therefore, combination of Shinkai's and our models may produce a model compound which is reactive and stable toward elec<sup>-</sup>ro-

3185

philic attack.

New models we synthesized are  $3-(N-\alpha-methylbenzyl)carbamoyl-1,4-dimethyl-1,4-dihydroquinoline (MeMQPH) and <math>3-(N-\alpha-methylbenzyl)carbamoyl-1,2,4-trimethyl-1,4-dihydroquinoline (Me_MQPH)$ . MeMQPH was prepared in essentially the same



procedure as described for the preparation of N- $\alpha$ -methylbenzyl-2,4-dimethyl-1propyl-1,4-dihydronicotinamide(6). However, Me<sub>2</sub>MQPH required a special technique for the synthesis: methylation of 3-(N- $\alpha$ -methylbenzyl)carbamoyl-2,4-dimethylquinoline did not undergo under usual condition. Instead, N-methylquinolinium derivative (Me<sub>2</sub>MQP<sup>+</sup>) was obtained by the reaction of 3-(N- $\alpha$ -methylbenzyl)carbamoyl-2,4-dimethylquinoline with methyl iodide quantitatively under 10,000 kg/cm<sup>2</sup> for a week at room temperature or in 55% yield under 2,000 kg/cm<sup>2</sup> for 14 days at 65°C(2).

Since 4-position is chiral, when  $S-\alpha$ -methylbenzylamine was employed for the synthesis,one of diastereoisomers of Me<sub>2</sub>MQPH with  $[\alpha]_{D}^{27}$  +210.3 (CHCl<sub>3</sub>,c = 0.203) was isolated by recrystallization.

Typically, the reduction was carried out with 1.1 : 1.0 (mol/mol) model to substrate ratio in the presence of appropriate amount of a Lewis acid in tetrahydrofuran at room temperature for 12 hours under an atmosphere of nitrogen. Results with Me<sub>2</sub>MQPH are summarized in the Table. The corresponding reduction with MeMQPH did not proceed at all under the same conditions except for the reduction of benzaldehyde, 25% of which was consumed after 7 hours at 65°C affording benzyl alcohol in 80% yield based on the consumed substrate. Thus, it is apparent that substitution of a methyl group on the 1,4-dihydropyridinering results in great improvement in the reactivity of a model compound,

It should be noted that the catalytic efficiency of a Lewis acid is not

Aldehyde	Lewis Acid	(equivalent)	Conversion,% <sup>a)</sup>	Yield of Alcohol, <sup>§b)</sup>
Benzaldehyde	BF <sub>3</sub> <sup>c)</sup>	2	31	0
	TiC1 <sub>4</sub>	2	24	25 <sup>d</sup> )
	A1C1 <sub>3</sub>	1	8	37.5 <sup>d</sup> )
	A1C1 <sub>3</sub>	2	75	96
	A1C1 <sub>3</sub>	3	73	97
	AlCl <sub>3</sub> e)	2	52	48
	ZrC1 <sub>4</sub>	2	59	5 <sup>d</sup> )
	SbC1 <sub>3</sub>	2	0	-
Croton aldehyde	A1C1 <sub>3</sub>	2	68	4 1
Cinnamyl aldehyde	A1C1 <sub>3</sub>	2	66 <sup>f</sup> )	35
Octanal	A1C1 <sub>3</sub>	2	79	2.5 <sup>g)</sup>

## Table. REDUCTION OF ALDEHYDES BY AN NAD(P)H-MODEL

a) Amount of substrate consumed. b) Yields were measured on VPC and based on consumed substrate. c) Solvent: THF + hexane(1:1 vol/vol), otherwise the reaction mixture is heterogeneous. d) The substrate decomposed into many unidentified products. e) Solvent: acetonitrile. f) The recovered aldehyde was consisted of 70% trans-and 30% cis-isomers. 3-Phenylpropanal was also formed in less than 1% yield. g) Acid-catalyzed aldol-condensation competes with the reduction affording undesired by-products.

proportional to the efficiency to form a complex with carbonyl compound: the latter efficiency increases in the order  $BF_3 < TiCl_4 < AlCl_3 < ZrCl_4 < SbCl_3(B)$ , whereas AlCl<sub>3</sub> shows the largest efficiency in the reduction. Thus, the Lewis acid in the reduction is not a simple electrophilic catalyst to polarize a carbonyl group, but it seems to play a role of a template to combine a substrate and model. The idea is in good agreement with the one proposed previously (2).

Yields of benzyl alcohol from benzaldehyde so far reported in relation to biomimetic reduction with 1 : 1 substrate to model ratio are 5 - 12%(4,9-11), which may prove the effectiveness of our model compound of new type.

Stereochemistry of the reduction and application to a variety of substrates are currently being investigated in our laboratory.

## REFERENCES

1. T. C. Bruice and S. J. Benkovic, in "Bioorganic Mechanisms," Vol. 2, W. A. Benzjamin, Inc., New York, N. Y., 1966, pp 301 - 349, Table 9-5.

2. A. Ohno, H. Yamamoto, and S. Oka, J. Am. Chem. Soc., 103, 2041 (1981) and references cited therein.

3. (a) S. Shinkai, H. Hamada, Y. Kusano, and O. Manabe, Bull. Chem. Soc. Jpn. ,52, 2600 (1979) ;(b) S. Shinkai, H. Hamada, Y. Kusano, and O. Manabe, J. Chem. Soc., Perkin II, 699 (1979).

4. S. Shinkai, H. Hamada, and O. Manabe, Tetrahedron Lett., 1397 (1979).

5. S. Yasui, K. Nakamura, A. Ohno, and S. Oka, Bull. Chem. Soc. Jpn., <u>55</u>, 196 (1982).

6. A. Ohno, M. Ikeguchi, T. Kimura, and S. Oka, J. Am. Chem. Soc., <u>101</u>, 7036 (1979).

7. We thank Prof. A. Sera of Kobe Univ. and Prof. S. Matsumoto of Kyoto Univ. for their help and instruction to use their high-pressure apparatus.

8. G. A. Olah and M. W. Meyer, in "Friedel-Crafts and Related Reactions," Vol. 1, G. A. Olah, Ed., Interscience Pub., New york, N. Y., 1963, pp 623 - 765. Table 37.

9. D. M. Stout, T. Takaya, and A. I. Meyers, J. Org. Chem., <u>40</u>, 563 (1975).
10. Y. Ohnishi and M. Kitami, *Tetrahedron Lett.*, 4033 (1978).

11. A. J. de Koning, H. J. Alberts-Jansen, J. Boersma, and G. J. M. van der Kerk, *Rec. Trav. Chim. Pays-Bas*, 99, 316 (1980).

(Received in Japan 24 April 1982)