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BEHAVIOUR OF NAD$^+$-MODEL COMPOUND WITH ALKOXIDES[1)]

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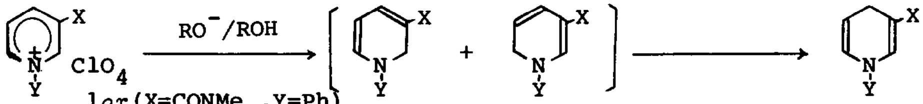
Non-enzymatic oxidations of alcohols by a model of NAD$^+$ is potentially interesting and important[2)]. Though, recently, oxidation of benzyl alkoxides by a pyridinium ion was remarkably demonstrated by Shirra and Suckling[3)], there are ambiguous points[4)], for example, their discussions are based on the production of the aldehyde with not confirming the formation of the 1,4-dihydropyridine. Now we wish to report behaviour of NAD$^+$-model compounds with alkoxides such as ethoxide, especially, on the base of the isolation of the 1,4-dihydronicotinamide.



1ox (X=$CONMe_2$, Y=Ph) — *1red*
2ox (X=$CONH_2$, Y=Ph) — *2red*
3ox (X=$SO_2N(CH_2CH_2)_2O$, Y=C_7H_{15}) — *3red*

All experiments described below were carried out with a H-type glass vessel separated by a breakable wall. Solutions of a pyridinium perchlorate and an alkoxide were mixed after the both solutions were throughly degassed by usual thawing-and-freezing method and sealed in a high vacuum. As a typical run, *1ox* (175mg, 0.54mmol) in dry acetonitrile(20ml) was kept in one arm of the vessel. In the other arm, was kept a dry and peroxide-free THF(10ml) solution of lithium ethoxide prepared from 0.2ml of ethanol and 0.25ml of 1.0 N hexane solution of BuLi. Both solutions were mixed and kept at 82°C for 24 hr. After the reaction, the mixture was concentrated *in vacuo* and the residue was column-chromatographed on basic alumina eluting with ethyl ether containing 0.2% of ethanol. From the first yellow eluate, 33mg of the 1,4-dihydronicotinamide, *1red*, was isolated. The structure of the product was identified by comparing its nmr spectrum with that of an authentic sample prepared by the dithionite reduction. The time-dependence of the yield of *1red* determined by high pressure liquid chromatography (HPLC) is shown in Figure 1, indicating the maximal yield of *1red* to be 28%. The yield in the reaction at room temperature for 3 days was 3.5%.

Methoxide, isopropoxide, and even *tert*-butoxide were found to be as effective as ethoxide. The reaction does not depend on the nature of the counter cation and its source; namely sodium and lithium alkoxides prepared from the corresponding metal are also able to be used.

Further, we attempted the reaction using the other model compounds and ethoxide. Reaction of *2ox* at room temperature for 33 hr gave *2red* in 12% yield together with the cyclic trimer[1] (in 53% yield). Shirra's model, *3ox*, in the reaction at 82°C for 16 hr afforded *3red* in 37% yield. In addition, by treating *p*-N,N-dimethylaminophenyl methoxide the conversion of *3ox* to *3red* was 34% after 16 hr at 82°C, but only 1.2% after 2 days at 25°C. Under more mild conditions (THF, 10^{-3}-10^{-5}M, at 25°C), the formation of *3red* could not be confirmed by HPLC[5].

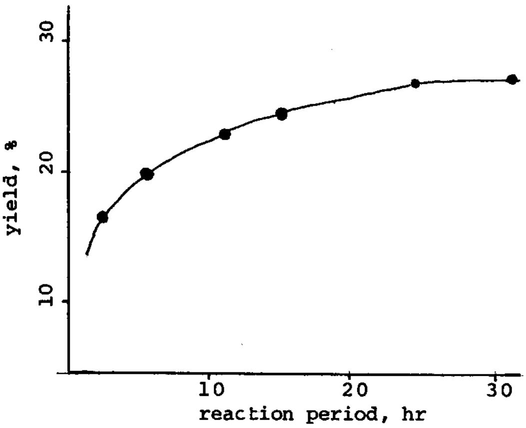


Fig. 1. Time-dependence of the formation of *1red* in the reaction of *1ox* and ethoxide at 82°C.

In order to know details for the formation of the 1,4-dihydronicotinamide, tracer experiments were carried out. The 1,4-dihydropyridine obtained from the reaction of *1ox* with CD_3OLi-CD_3OH did *not* contain a deuterium atom. On the other hand, the reaction in CH_3OLi-CH_3OD system gave the mixture of 2-deuterio- and 6-deuterio-1,4-dihydronicotinamide which were confirmed by its nmr spectrum.

Although the formation of the 1,4-dihydronicotinamide should show that the reaction involves the *net hydride transfer*, the results of tracer experiments suggested that the present reaction can *not be a model* for alcohol dehydrogenase reactions. The incorporation of alcoholic proton into the 2- or 6-positions of the pyridinium ring suggests that the 1,2-and 1,6-dihydropyridines deuterated on 2- and 6-positions, respectively, are *primary products* following the intermolecular isomerization[6] with excess of pyridinium cation to the 1,4-isomer.

References and footnote

1) Y. Ohnishi, H. Minato, K. Okuma, and M. Kobayashi, Chem. Letters, 525(1977).

2) K. Wallenfels and W. Hanstein, Angew. Chem. Int. Ed., **4**, 869(1965).

3) A. Shirra and C. J. Suckling, Tetrahedron Letters, 3323(1975) and J. Chem. Soc. Perkin II, 759(1977).

4) Y. Ohnishi and M. Kitami, preceding paper in this issue.

5) The reaction was carried out under atomosphere of argon. A large amount of the benzaldehyde was detected by HPLC. It appears that the aldehyde is formed by air-oxidation of the alkoxide.

6) Y. Ohnishi and S. Tanimoto, Tetrahedron Letters, 1909(1977).

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