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REVERSIBLE HYDRIDE TRANSFER FROM 1-METHYL-1,4-DIHYDRONICOTINAMIDE (1,4-MeNDH) TO $MeND^+$ IODIDE YIELDING 1,6-MeNDH

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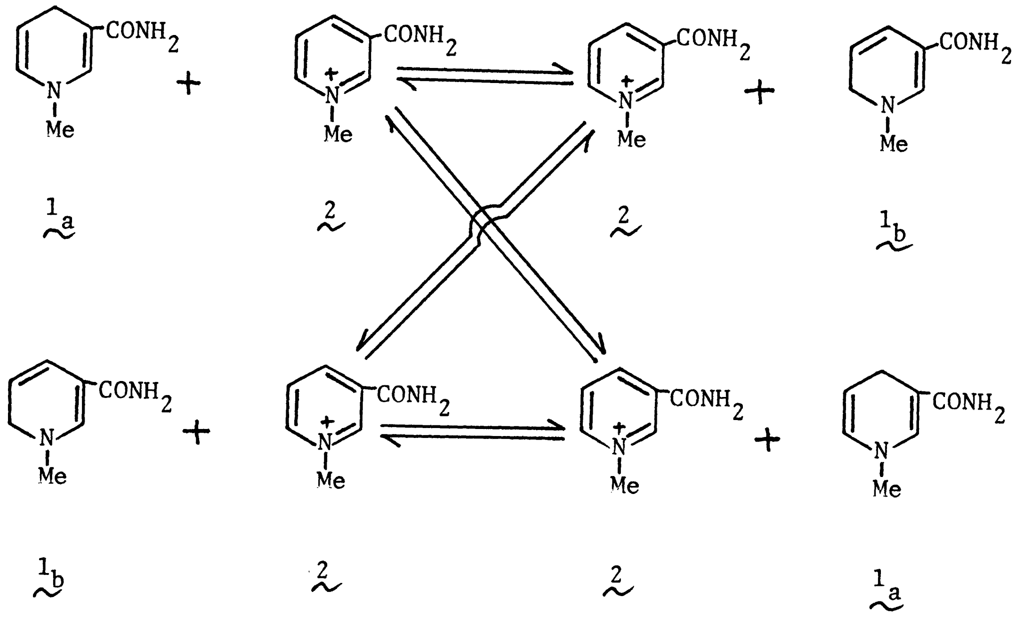
The reaction of 1-methyl-1,4-dihydronicotinamide (1,4-MeNDH) with $MeND^+$ in D_2O at 34° was found to yield 1,6-MeNDH, and the reaction of 1,6-MeNDH with $MeND^+$ was found to yield 1,4-MeNDH. An equilibrium was established between 1,6-MeNDH(18%) and 1,4-MeNDH(82%) when either of the 1-methyldihydronicotinamides was mixed with a catalytic amount of $MeND^+$.

Recently van Bergen, Mulder, and Kellogg reported irreversible hydride transfer from 1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine(I_a) to the 2-position of 1,2,6-trimethyl-3,5-dicarboethoxypyridinium perchlorate(II) at 60°, forming 1,2,6-trimethyl-3,5-dicarboethoxy-1,2-dihydropyridine(I_b).[1] We have found that 1-methyl-1,4-dihydronicotinamide(1,4-MeNDH) (1_a), a compound as a model closer to NADH, transfers its hydride to the 6-position of $MeND^+$ iodide (2) reversibly.

When 1_a (1 equiv) and 2 (0.05 equiv) were dissolved in D_2O at 34°, the PMR spectrum of the solution indicated the decrease of the concentration of 1_a and the formation of 1,6-MeNDH (1_b), whose concentration gradually increased ($[1_b]/[1_a]$ = 3/97, 19/81, and 19/81 after 30, 1440, and 3000 min. respectively); $1_a(D_2O)$, δ 2.92 (CH_3), 2.98-3.08 (CH_2); $1_b(D_2O)$, δ 2.84 (CH_3), 4.02-4.12(CH_2). Because of complex spin couplings, the PMR absorptions of the ring hydrogens of 1_a and 1_b are complex, and this makes it difficult to recognize the formation of 1_b in the presence of a greater amount of 1_a.

However, the carbon-13 NMR spectrum of the reaction mixture very clearly showed the appearance and increase of the concentration of 1_b. The Figure shows the ^{13}CMR spectrum of the mixture after 50 hr at 34°. Chemical shifts were assigned by using the chemical shifts of related known compounds and the off-resonance proton decoupling technique.[2] An authentic sample of 1_b was synthesized by applying the method described for the preparation of 1-propoxymethyl-1,6-NDH.[5]

The reactions which took place in the mixture are probably represented by the following scheme.



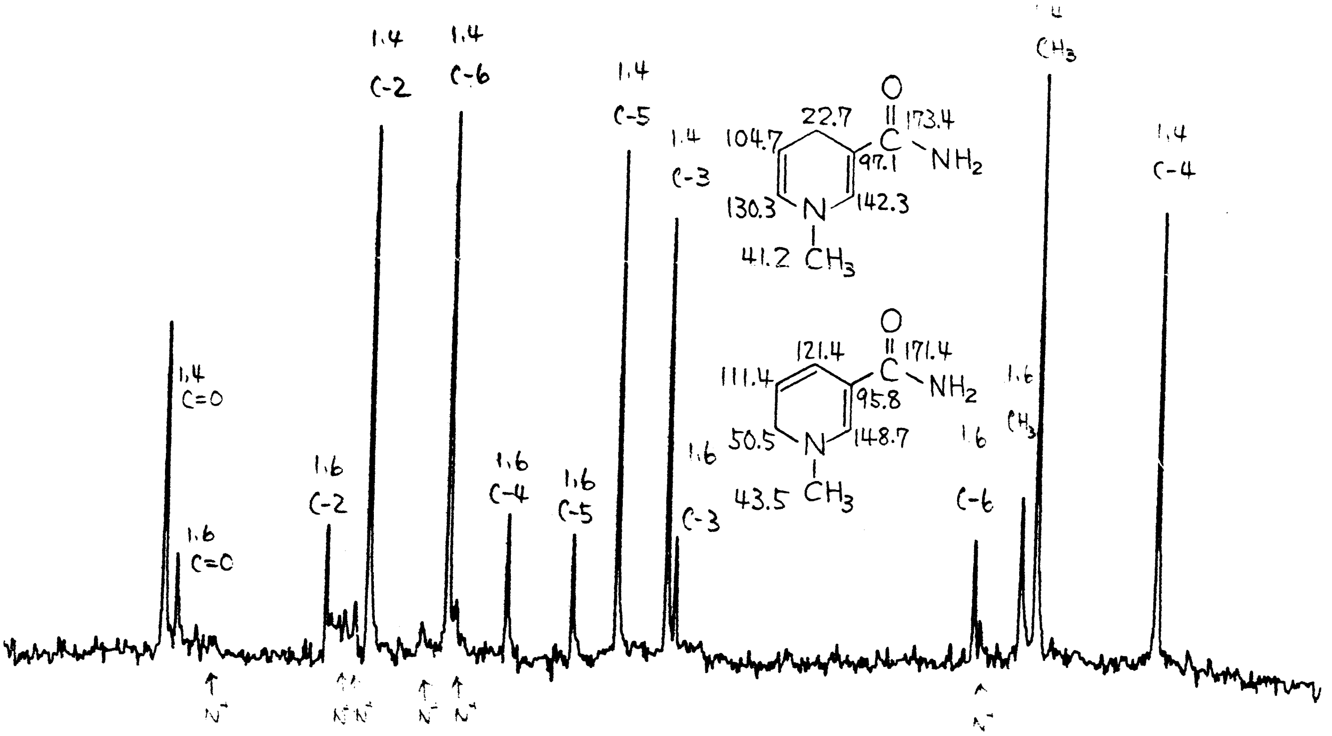
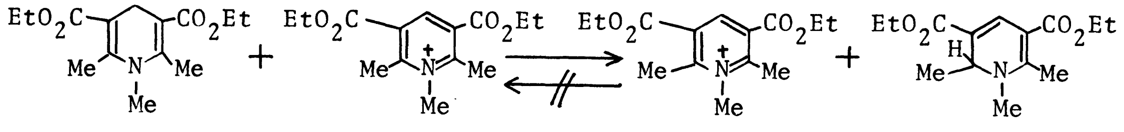


Figure. ^{13}CMR spectrum of a mixture of 1_a (1 equiv.) and 2 (0.05 equiv.) in D$_2$O after 50 hr at 34°. (Chemical shifts values are in ppm downfield from TMS.Very small peaks are due to 2.)

The fact that an equilibrium was established between $\mathbf{1_a}$ and $\mathbf{1_b}$ indicates that $\mathbf{1_b}$ does reduce $\mathbf{2}$ and regenerate $\mathbf{1_a}$. If the reaction ($\mathbf{1_b}$ + $\mathbf{2} \longrightarrow \mathbf{2}$ + $\mathbf{1_a}$) did not take place, all the $\mathbf{1_a}$ must have been converted to $\mathbf{1_b}$ by the reaction ($\mathbf{1_a}$ + $\mathbf{2} \longrightarrow \mathbf{2}$ + $\mathbf{1_b}$) after elapse of sufficient time. Van Bergen et al.[1] reported that in the case of their Hantzsch esters the reaction ($\mathbf{I_b}$ + $\mathbf{II} \longrightarrow \mathbf{II}$ + $\mathbf{I_a}$) does not take place and all the $\mathbf{I_a}$ are converted to $\mathbf{I_b}$ quantitatively by the reaction ($\mathbf{I_a}$ + $\mathbf{II} \longrightarrow \mathbf{II}$ + $\mathbf{I_b}$): once $\mathbf{I_b}$ is formed, it remains as such and hydride can no longer escape from it.



$\mathbf{I_a}$ $\mathbf{II}$ $\mathbf{II}$ $\mathbf{I_b}$

In order to ascertain that $\mathbf{1_b}$ does reduce $\mathbf{2}$, a mixture of $\mathbf{1_b}$ (0.49 equiv)[6] and $\mathbf{1_a}$ (0.51 equiv) was mixed with $\mathbf{2}$ (0.05 equiv) in D_2O at 34°. The composition changed as expected ($[\mathbf{1_b}]/[\mathbf{1_a}]$ = 49/51, 42/58, 33/67, 17/83, and 17/83 after 0, 7, 80, 1170, and 1530 min, respectively). In the absence of $\mathbf{2}$, the composition of the mixture of $\mathbf{1_b}$ and $\mathbf{1_a}$ did not change after 1530 min.

It is of interest to note that methylene hydride at C-4 ($\mathbf{1_a}$ and $\mathbf{I_a}$) and methylene hydride at C-6 ($\mathbf{1_b}$) are usable for reduction but methine hydride of $\mathbf{I_b}$ at C-2 is not usable for reduction. The inertness of the methine hydride of $\mathbf{I_b}$ even at 60° is probably ascribable to steric hindrance, and it seems reasonable that the methylene hydride of $\mathbf{1_b}$ which is not sterically hindered is labile at 34°.

Since the structure of NADH in living cells is closely related to that of 1,4-MeNDH, it is possible that NADH in living cells transfers part of its hydride to the 6-position of NAD^+ forming 1,6-NADH, and an equilibrium similar to that between 1,4- and 1,6-MeNDH is established between 1,4-NADH (major) and 1,6-NADH (minor), which possess sterically unhindered methylene hydride at C-4 and C-6, respectively. On the other hand, if NADH in living cells does not contain any 1,6-NADH at all, the prevention of the hydride transfer to the 6-position must be ascribed to actions of enzymes.

The results of our investigation point out that (1) the 6-position of $\mathbf{2}$ does accept a hydride at 34°, (2) the 1,6-MeNDH produced does reduce another molecule of $\mathbf{2}$, and (3) an equilibrium is established between 1,4-MeNDH (82%) and 1,6-MeNDH (18%) when a small amount of $MeND^+$ is present in the medium.

Ludowieg and Levy studied the reaction between 1,4-PrNDH (1-propyl-1,4-dihydronicotinamide) and $PrND^+$.[7] Although they clearly showed that the 4-hydride (tritium) of 1,4-PrNDH is transferred to $PrND^+$, they did not report the formation of 1,6-PrNDH, and only described that in mixtures left for a few hours at room temperature it was possible to identify a third component on paper chromatography. The component is most likely 1,6-PrNDH.

Fowler reported that an equilibrium mixture of unsubstituted N-methyldihydropyridine contains 7.7% of the 1,2-dihydro isomer.[8] This figure is reasonably compared with that in an equilibrium mixture of MeNDH (the 1,6-dihydro isomer, 18%).

REFERENCES AND NOTES

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5. A. C. Lovesey and W. C. Ross, J. Chem. Soc., (B), 1969, 192; the application of the method to the synthesis of 1,6-MeNDH resulted in the formation of a mixture of 1,6-MeNDH and 1,4-MeNDH ($[\mathbf{1}_\mathrm{b}]/[\mathbf{1}_\mathrm{a}]$ = 49/51). The PMR and ^{13}CMR spectra of the mixture were consistent with the structures of $\mathbf{1}_\mathrm{a}$ and $\mathbf{1}_\mathrm{b}$. Attempts for obtaining pure $\mathbf{1}_\mathrm{b}$ were not successful.
6. Since pure $\mathbf{1}_\mathrm{b}$ is not available,[5] a mixture of $\mathbf{1}_\mathrm{b}$ and $\mathbf{1}_\mathrm{a}$ was used.
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