Communications to the Editor

Hydride Mobility in Pyridinium Salt–Dihydropyridine Mixtures. A Biomimetic Pyridine Nucleotide Transhydrogenation

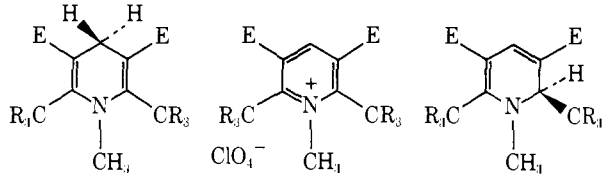
Sir:

The discovery by Kaplan, Colowick, and Neufeld[1] in 1953 of a mitochondrial pyridine nucleotide transhydrogenase responsible for catalysis of eq 1 has been followed by appreciation of the fact that this reaction forms an important link in oxidation–reduction processes in the cell.[2]

$$\mathrm{NADH} + \mathrm{NDP^+} \underset{\text{enzyme}}{\overset{\text{enzyme}}{\rightleftarrows}} \mathrm{NAD^+} + \mathrm{NADPH} \qquad (1)$$

That the reaction involves the direct transfer of hydride has been demonstrated and moreover much is becoming clear of the mechanism by which the enzyme works.[3,4] Of special pertinence, however, is that the fundamental chemical transformation involved, hydride transfer from a 1,4-dihydropyridine to the 4-position of a pyridinium salt, is a recognized organic reaction capable of proceeding without catalysis by an enzyme (albeit usually at relatively high substrate concentrations).[5] It is a patent necessity that this process be better understood not only for reasons of aiding our understanding of the workings of the enzyme but also as a preliminary to the effective application of 1,4-dihydropyridines to synthetic goals.

Working towards this end we have uncovered the details of the remarkably ready and previously undetected wanderings of a hydride among **1**–**3**.[6] The utility of Hantzsch ester derived 1,4-dihydropyridines as nicotinamide nucleotide models is well recognized.[7-10] The stability of these compounds as well as the symmetry present with the resulting simplification of the ^{1}H NMR spectra was essential for our purposes.



1 (E = $CO_2C_2H_5$)
a, R = H
b, R = D

2

3

In methanol at 60° a sample of **1a** in the presence of **2a** was converted quantitatively to **3a** within 20 h.[11] This catalytic conversion (eq 2) of a 1,4-dihydropyridine to its 1,2-isomer is not detectably reversible at 60°.

$$\textbf{1a}\ (10\ \text{equiv}) + \textbf{2a}\ (1\ \text{equiv}) \xrightarrow{k_i} \textbf{3a}\ (10\ \text{equiv}) + \textbf{2a}\ (1\ \text{equiv}) \qquad (2)$$

The conversion of **1** to **3** does not occur in the absence of **2**. As seen in Figure 1, sharp isosbestic points are present. On running the reaction under the same conditions in CD_3OD or CH_3OD, **3** was again formed quantitatively, but it contained 4.7 deuterons in the 2,6-methyl groups. However, within the limits of instrument sensitivity the 2-position was substituted exclusively with a proton and not a deuteron.[12] Under these conditions in blank experiments **3a** incorporates in 15 h no deuterium in the 2,6-methyl groups, **1a**, 1.2 deuterons after 15 h, and **2a**, 4.1 deuterons after 15 h. This implies clearly that **3** is derived from hydride transfer to pyridinium salt **2**, a point established with certainty by deuterium labeling (see below).

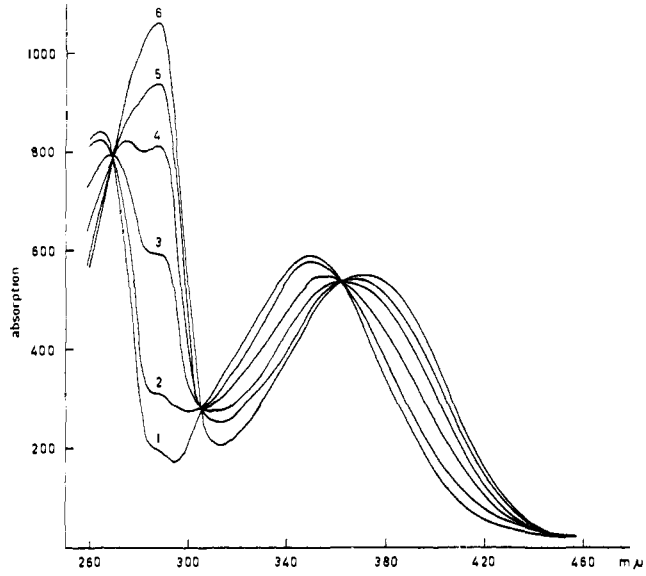


Figure 1. Uv recordings of the reaction of **1a** with **2a** (0.33 and 0.06 M in acetonitrile) at 70.2°. Reaction time: (1) 2 min; (2) 21 min; (3) 81 min; (4) 142 min; (5) 188 min; (6) 233 min.

The rearrangement of eq 2 is accompanied by an even faster "blind" exchange. This was revealed by preparing **2b** by repeated exchange of **2a** in C_2H_5OD with a trace amount of triethylamine. The sample of **2b** used contained 5.88 deuterons in the 2,6-methyl groups. On mixing equimolar amounts of **1a** and **2b** at ambient temperature in C_3D_6O and monitoring the ^{1}H NMR spectrum, there was observed that the absorption for the 2,6-methyl groups of **1a** at δ 2.38 decreased and an absorption appeared at δ 3.16 arising from the 2,6-methyl groups of **2a** (Figure 2). The combined integration of these absorptions was for six protons. A sample of **1b** (monodeuterated in the 4-position) was prepared by reduction of **2b** in D_2O; reaction with **2a** produced **1a** (chiefly diproto- in the 4-position, the isotope effect has not been measured accurately). These combined observations establish the existence of the (normally "blind") reversible process of eq 3.

$$\textbf{1a}\ (1\ \text{equiv}) + \textbf{2b}\ (1\ \text{equiv}) \underset{k_r}{\overset{k_f}{\rightleftarrows}} \textbf{2a}\ (1\ \text{equiv}) + \textbf{1b}\ (1\ \text{equiv}) \qquad (3)$$

No detectable amounts of **3** are formed but on raising the temperature to 60° a mixture of **1a** and **2b** produces **3b** and not **3a** demonstrating that indeed a hydride is transferred *inter*molecularly to the 2-position of the pyridinium salt. In a mixture of **3a** and **2b** no "blind" exchange occurs.

At 25° for eq 3, K_{eq} is 0.84, $k_f = 1.70 \times 10^{-4}$, and $k_r = 2.01 \times 10^{-4}$ l. mol^{-1} s^{-1}. The slight preference for deuterium to reside at equilibrium in the pyridinium salt is in accord with inductive effects for this isotope.[13] Measured by ^{1}H NMR spectroscopy over the temperature range 22.0–38.0° (five points, correlation coefficient for Arrhenius plot

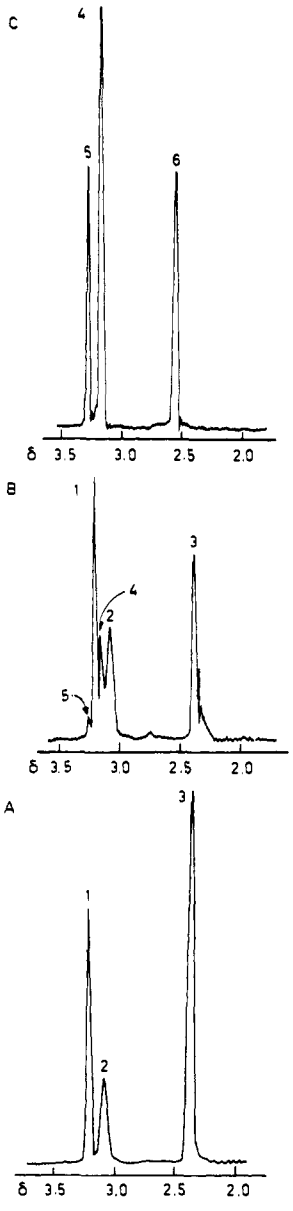


Figure 2. ^{1}H NMR recordings. (A and B) Reaction between 3,5-dicarboethoxy-1,2,6-trimethyl-1,4-dihydropyridine (**1a**) and 3,5-dicarboethoxy-2,6-di(trideuteriomethyl)-1-methylpyridininium perchlorate (**2b**) in acetone-d_6 (concn 0.3 mol/l. each) at 23°. A, zero time; B, after 229 min of reaction time. (c) The same reaction between **1a** and unlabeled **2a** after 21 h at 60°; no **1a** remains. Peaks: (1) 1,4-DHP, N-CH_3; (2) 1,4-DHP, CH_2; (3) 1,4-DHP, 2,6-CH_3; (4) pyr salt, 2,6-CH_3; (5) 1,2-DHP, N-CH_3; (6) 1,2-DHP, 6-CH_3.

0.995) $\Delta H^{\ddagger}$ was found to be 21.4 kcal mol^{-1} and $\Delta S^{\ddagger}$ was −3.7 eu. Kinetic data were analyzed by standard methods.[14]

Despite the fact that the "blind" reaction of eq 3 proceeds faster, the activation energy is higher than for the isomerization of eq 2. Measured in acetonitrile using uv spectroscopy to follow the isomerization of **1** to **3** over the temperature range 55.0–74.8° (seven points, correlation coefficient for Arrhenius plot 0.990), $\Delta H^{\ddagger}$ = 16.9 kcal mol^{-1}; the rate compensation is found, however, in the low $\Delta S^{\ddagger}$ of −20.9 eu.[15] The kinetic parameters for the processes of eq 2 and 3 lie in the same order of magnitude as reported in the literature for chemically related reactions.[16]

Ignoring the difference in solvents[17] and extrapolating to 25° the 4-position of **2** accepts hydride 17 times more rapidly than the 2(6)-positions taking the statistical factor of two into account. The 2(6)-positions of pyridinium salts are calculated to be more electron deficient than the 4-position[18] in accord with the observed ordering of $\Delta H^{\ddagger}$'s. However, the reactivity is in fact controlled by the large and unanticipated differences in activation entropies. It remains to be seen whether this effect is general. The kinetic data support fully a reaction model wherein a hydride is transferred by a second-order kinetic process. No evidence for the formation of charge transfer complexes could be adduced. The possibility of reaction via initial electron-transfer pathways[19] cannot be eliminated.

A point worthy of emphasis is the demonstration of the structural effect that the 1,4-dihydropyridine is an excellent hydride donor whereas the 1,2-isomer is unreactive under mild conditions and serves only as a trap from which hydride can no longer escape. This and other points are explored further in the following communication.

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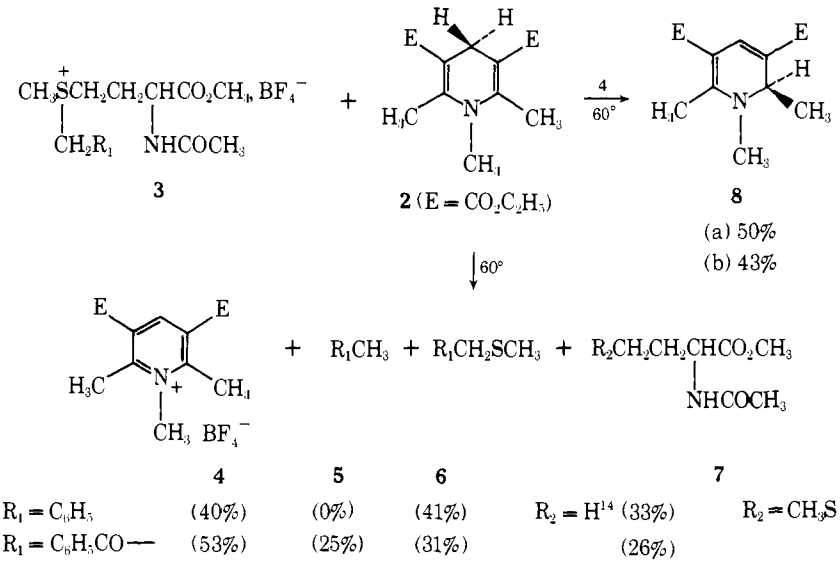
Hydride Transfer from NADH Models to sp^3-Hybridized Carbon. Competition with Enamine Alkylation

Sir:

Following the initial recognition that reactions of simple 1,4-dihydropyridines,[1] including the readily accessible Hantzsch esters,[2,3] can be used to mimic certain aspects of hydride transfer from NAD(P)H, an avalanche of examples has accumulated in the literature.[4] Conspicuously absent (to the best of our knowledge) among these many reactions is any demonstration of reduction of a sp^3-hybridized carbon via (formal) nucleophilic displacement by hydride derived from the dihydropyridine. We report here the discovery of examples of such reactions using either sulfonium salts or activated halides as substrates. For several important biological processes NAD(P)H reduction of sp^3-carbon provided with a good leaving group may reasonably be postulated (direct reduction of a free carbonium ion being less likely). Examples suggest themselves in the in vivo (overall) methylations by *S*-adenosylmethionine (**1**)[5] of unactivated double bonds in fatty acids (the reaction, however, involves initial methylation and subsequent reduction)[6a,b] and steroids[7,8] as well as the presqualene alcoholpyrophosphate–squalene interconversion[9] and related models of monoterpene biosynthesis.[10]

When **2** was allowed to react in C_3D_6O at 60° with the protected methionine sulfonium salts (**3a, b**),[11,12] a quantitative reaction ensued with the results shown in Scheme I.[13] The desired reduction is clearly taking place. With benzyl sulfonium salt (**3a**), hydride incorporation is (surprisingly)

Scheme I



		4	**5**	**6**	**7**	
(**3a**)	$R_1 = C_6H_5$	(40%)	(0%)	(41%)	$R_2 = H$[14] (33%)	$R_2 = CH_3S$ (0%)
(**3b**)	$R_1 = C_6H_5CO$—	(53%)	(25%)	(31%)	(26%)	(27%)

Table I. Reductions by 3,5-Dicarboethoxy-1,2,6-trimethyl-1,4-dihydropyridines (**2**)[13]

	Sulfonium salt $R_1S^+R_2R_3$				% reduction products		% transhydrogenation[4c]		
	R_1	R_2	R_3	% oxidation product **4**	R_1H	R_2–S–R_3	1,2-DHP	**8**	Unreacted substrate
9	$C_6H_5COCH_2$	CH_3	CH_3 X^- [a]	40	33	33	53	**9**	57
10	$C_6H_5COCH_2$	CH_3	C_6H_5 Y^-	37	34	38	52	**10**	57
11	$CH_2CO_2CH_3$	CH_3	C_6H_5 Y^-	13	10	14	70[b]	**11**	75
12	CH_3	C_6H_5	C_6H_5 X^-	18	[c]	20	86	**12**	86
13	$C_6H_5CH_2$	CH_3	CH_3 Y^-	3–5	3–5[d]	3–5	86[e]	**13**	93
14	$C_6H_5CH_2$	CH_3	C_6H_5 Y^-	42	11[d]	82	11	**14**	8
15[g]	$C_6H_5CH_2$	C_6H_5	C_6H_5 Y^-	54	3[d]	100	[f]	**15**	[f]
Alkyl halides									
16[g]	$BrCH_2COC_6H_5$			39	35 (**5b**)		35[h]	**16**	71
17[g]	$BrCH(CN)_2$			63	70[i] (**18**)		[f]	**17**	[f]

[a] $X^- = ClO_4^-$, $Y^- = BF_4^-$, solvent C_3D_6O, temp 60°. [b] **2** remained in 11% yield. [c] No attempts were made to detect methane. [d] The radical coupling product, bibenzyl, was not present. [e] **2** remained in 10% yield. [f] Not detectable. [g] Carried out at room temperature. [h] **2** remained in 26% yield. [i] Lower limit for yield.