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HYDRIDE TRANSFER FROM 1,4-DIHYDROPYRIDINES TO PYRIDINIUM SALTS

ASSESSMENT OF STRUCTURAL AND ENERGETIC FACTORS WITH HANTZSCH ESTER DERIVED COMPOUNDS[1]

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Abstract—Hydride exchange occurs between 3,5 - di(alkoxycarbonyl) - 1,4 - dihydropyridines and their corresponding pyridinium salts. For the case of 1,2,6 - trimethyl - 3,5 - di(ethoxycarbonyl) - 1,4 - dihydropyridine in the presence of the structurally corresponding pyridinium perchlorate, hydride is transferred to the 4-position of the pyridinium salt in a reversible "blind" reaction as revealed by deuterium labeling experiments and to the 2,6-positions irreversibly to afford 1,2,6 - trimethyl - 3,5 - di(ethoxycarbonyl) - 1,2 - dihydropyridine as final product. Removal of the methyl groups at the 2,6-positions, i.e. 1 - methyl - 3,5 - di(methoxycarbonyl) - 1,4 - dihydropyridine and its structurally corresponding pyridium perchlorate, causes hydride transfer to become completely reversible. Substitution of the 4-position with Me, i.e. 1,2,4,6 - tetramethyl - 3,5 - di(methoxycarbonyl) - 1,4- -dihydropyridine and its corresponding pyridinium perchlorate leads to cessation of hydride transfer; the same is true for the analogous 4-phenyl (and substituted phenyl) compounds. However, these 1,4-dihydropyridines are capable of transferring hydride at reasonable temperatures to less highly substituted pyridinium salts. Activation parameters for some of these hydride transfers have been determined, mechanistic conclusions are presented, and the consequences of these observations for experiments with "model" NADH compounds are discussed.

An essential biochemical process is the enzyme mediated exchange of hydride between NADH and $NADP^{\oplus}$ (eqn 1).[2,3]

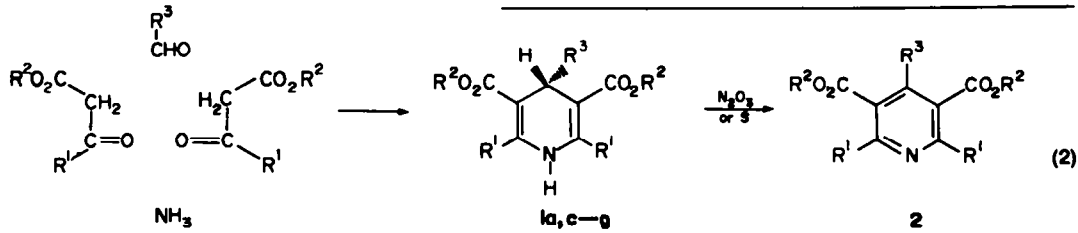
$$NADH + NADP^{\oplus} \rightleftarrows NAD^{\oplus} + NADPH \qquad (1)$$

The chemical transformation involved, transfer of hydride from a 1,4-dihydropyridine to a pyridinium salt, has been demonstrated by several groups to be also an intrinsic organic reaction which proceeds, albeit more slowly, in the absence of a catalyst.[4-6] The existence of these exchanges raises questions concerning possible isomerism in the position of attachment of hydride to the dihydropyridine ring. This point is particularly relevant because in any reaction wherein a 1,4-dihydropyridine reduces a substrate, pyridinium salt is formed. The presence of the pyridinium salt can have a substantial effect on the further course of the reaction.[7]

To define the structural features governing this exchange reaction we have investigated a series of dihydropyridine/pyridinium salt mixtures. These investigations have been confined for the most part to pyridines available through the Hantzsch dihydropyridine synthesis (eqn 2). The Hantzsch condensation goes well only with ammonia rather than substituted amines as component; this means that to obtain compounds structurally analogous to NADH and $NAD^{\oplus}$ (i.e. that loss of hydride from the dihydropyridine affords *pyridinium salts*) the N atom of **2** must be alkylated. The required methylated pyridinium salts **3a–g** (for all experiments the counterion was $ClO_4^{\ominus}$ obtained by precipitating the pyridinium salt from saturated $NaClO_4$ solution), 1,4-dihydropyridines **4a–g** and 1,2-isomers **5a–c** were obtained *via* the routes shown (eqn 3). The choice of these Hantzsch ester derived systems is based both on the possibility for systematic structural variation and the symmetry of these compounds, which greatly simplifies the ^1H NMR spectra required for following the course of hydride transfer reactions.

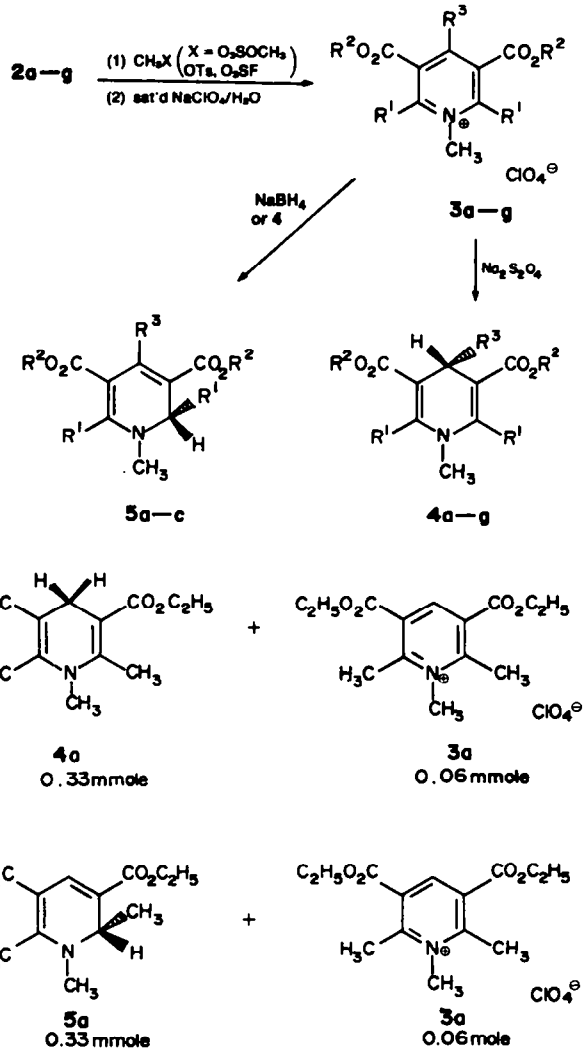
RESULTS

In preliminary experiments it was established that the pyridinium salt **3a** in catalytic quantities causes **4a** to isomerize irreversibly to the 1,2-isomer **5** (eqn 4). ^1H NMR spectroscopy is extremely useful for following the reaction since all absorptions for **3–5a** can be distinguished in mixtures.[9] The reaction proceeds quantitatively in CD_3CN or CD_3COCD_3. The results shown in



(2)

a: $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = H$
b: $R^1 = R^3 = H$, $R^2 = CH_3$[6]
c: $R^1 = R^3 = CH_3$, $R^2 = CH_3$
d: $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = C_6H_5$
e: $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = 4\text{-}CH_3OC_6H_4$
f: $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = 4\text{-}CH_3C_6H_4$
g: $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = 4\text{-}ClC_6H_4$



(3)

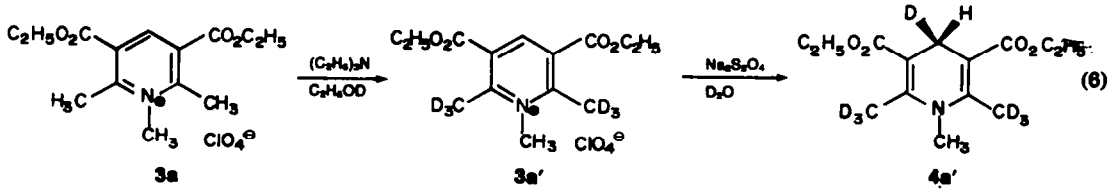
(4)

eqn (4) are typical; this reaction carried out at 70.2° shows sharp isobestic points at 269 nm, 305 nm and 363 nm. There is no experimentally detectable rearrangement of **4a** in the absence of pyridinium salt; the rearrangement shown in eqn (4) is also not demonstrably reversible up to 100° (decomposition sets in). Followed by either ^{1}H NMR or UV spectroscopy good apparent first-order kinetics are found. The first-order constants are doubled and halved, respectively, on doubling or halving the concentration of **3a** indicating that second-order kinetics (catalyzed first order reaction) are in fact followed (eqn 5).

$$\text{rate} = k_2[\mathbf{3a}][\mathbf{4a}] \qquad (5)$$

In order to examine better the mechanisms of the reactions occurring in this system, labeled compounds were prepared. A sample of **3a** was exchanged repeatedly with EtOD in Et_3N; this provided **3a'** containing minimally 5.88 deuterium atoms (98% incorporation) in the 2,6-methyl groups (eqn 6).[10] Reduction of **3a'** in D_2O with $Na_2S_2O_4$ gave **4a'** bearing 5.81 deuterons in the 2,6-Me groups and 0.8 D atoms at the 4-carbon.

On being allowed to stand at room temperature extensive changes occur in the ^{1}H NMR spectrum of an equimolar mixture of **3a'** and nondeuterated **4a**. The nondeuterated pyridinium salt **4a** appears and the concentration of **4a''** (no deuterium at the 4-position) increases. Clearly the reaction of eqn (7) to the right must be taking place. The reverse reaction was demonstrated by allowing **4a'** (monodeuterated at 4-position) to



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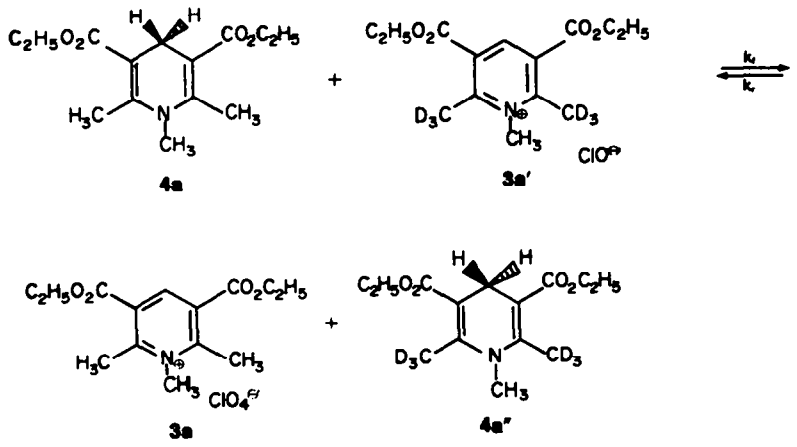


(7)

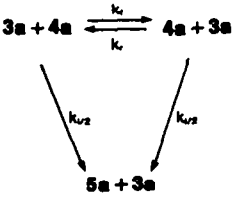
$$\left(\frac{k_f}{k_r}\right)^{25°} = Keq^{25°} = \frac{1.70 \times 10^{-4}\ \text{mole liter}^{-1}\ \text{sec}^{-1}}{2.01 \times 10^{-4}\ \text{mole liter}^{-1}\ \text{sec}^{-1}} = 0.84$$

react with **3a**; **4a** was formed cleanly. Only hydride transfer from **4a'** could be observed; integration data are, however, not sufficiently accurate to allow determination of the deuterium isotope effect. The individual rate constants k_f and k_r were derived from solution of the kinetic equation applicable for this type of reversible process.[11] Ignoring any secondary deuterium isotope effect with **4a'** $K_{eq}^{25°}$ is 0.84 for the exchange of eqn (7). Note that this is an experimentally unobservable "no reaction–reaction" if unlabeled compounds are used. Deuterium prefers to reside at equilibrium in the positively charged pyridinium salt consistent with arguments for lesser steric requirements and possible electron donation effects relative to hydrogen for this isotope.[12]

At 67° isomerization sets in at a rate competitive with that for "blind" exchange. A mixture of **4a** (0.3 mmole) and **3a'** (0.3 mmole) dissolved in 1 ml CD_3COCD_3 and held for 1 hr at 25° and thereafter for 1 hr at 67° afforded the product mixture shown in eqn (8). The products were identified and concentrations determined by analysis of the ^1H NMR spectra. The formation of isomerization product **5a'** bearing deuterium label clearly indicates that hydride transfer is intermolecular. Nonlabeled **5a** is formed through the "blind" exchange reaction followed by reduction of **3a** by **4a'** (the reactions of nonlabeled **3a** and **4a** and labeled **3a'** and **4a'** doubtlessly lead also to **5a** and **5a'**, respectively).

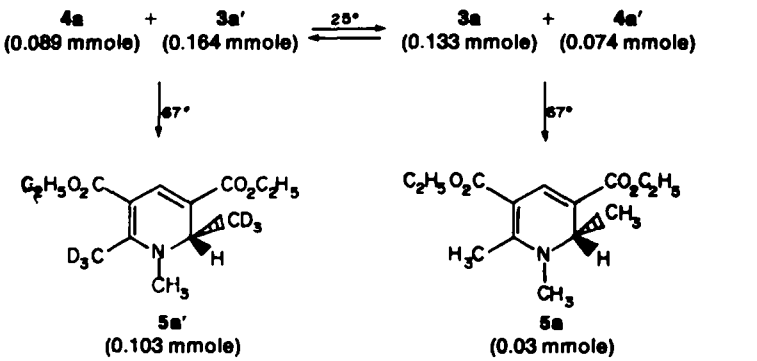
Further evidence for the intermolecular nature of the isomerization is provided from a reaction of unlabeled **3a** and **4a** in CD_3OD carried out for 15 hr at 60°. There was formed **5a** bearing 1.0 protium at the 2-position as ascertained from repeated integration of the 100 MHz ^1H NMR spectrum. Deuterium incorporation in the 2,6-Me groups was found but the mass spectrum indicated the absence of any d_7 species. The deuterium exchange is intrinsic to 2,6-Me groups; when allowed to stand in CD_3OD for 15 hr at 60° **3a** incorporated 2.1 deuterium, **4a** 1.2 deuterium, and **5a** no D atoms.

The kinetic behavior of the system **3–5a** is summarized in Scheme 1; "blind" exchange is reversible but isomerization to the 1,2-dihydro isomer **5** is irreversible and leads to eventual cessation of exchange.

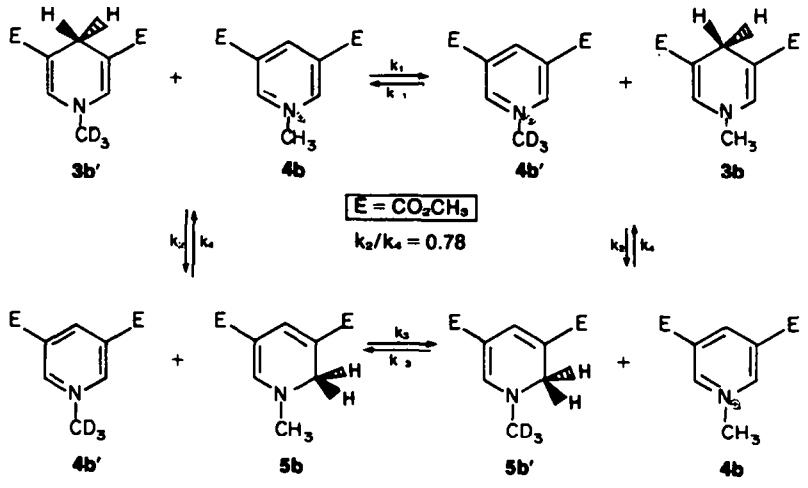


Scheme 1.

Removal of the 2,6-methyl groups from the (dihydro)pyridine ring has a large kinetic effect; the isomerization reactions become fully reversible as exemplified in Scheme 2 wherein deuterium labeled compounds are used. The labeled compounds were prepared as shown in eqn (9).

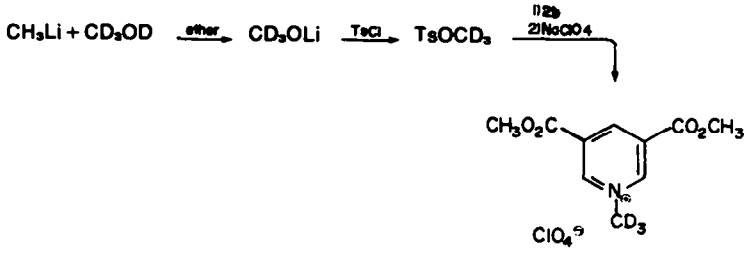


(8)



$k_1(25°) = 1.4 \times 10^{-2}$ liter mol^{-1} sec^{-1}
$k_2(25°) = 5.6 \times 10^{-4}$ liter mol^{-1} sec^{-1}
$k_4(25°) = 7.2 \times 10^{-4}$ liter mol^{-1} sec^{-1}

Scheme 2.



(9)

The equilibria of Scheme 2 represent an involved kinetic situation that we were only partially able to unravel. The assumption is made that any secondary D isotope effect involved with N-(trideuteriomethyl) compounds will be negligibly small, at least for the purpose of these measurements. At room temperature the equilibrium **5a/3a** is 0.78 very slightly is favor of the 1,4-dihydro isomer in agreement with observations on less heavily substituted systems.[13] The rate constants k_1 for "blind 4,4-exchange", k_2 for 4→2 isomerization, and k_4 for 2→4 isomerization could be evaluated independently and are shown in Scheme 2. Despite repeated attempts we were unable to extract a reliable value for k_3, the rate constant for "blind 2,2-exchange". The rate of 2→4 isomerization was of the same order of magnitude as for the blind exchange and we were unable to separate kinetically these two processes.

It was noted that on mixing 1,2-dihydro isomer **5b** with pyridinium salt **3b** in acetonitrile (both concentrations *ca* $5 = 10^{-2}$ M) that the solution took on an orange color, λ_{max} 500 nm. This color persisted for several minutes and then gradually disappeared. Representative data are given in Fig. 1. If this color were to arise from the formation of an intermediate in the rearrangement of 1,2-dihydropyridine to the 1,4-isomer, the intermediate thereafter decomposing to give 1,4-dihydropyridine, then a lag period in the rate of rearrangement would be anticipated. Because of the high concentrations required to obtain a reasonable absorption for the intermediate and high extinction coefficients of the dihydropyridines, ultra-violet measurements proved impractical. Dependable measurements of the rate of appearance of 1,4-dihydropyridine could be obtained from the fluorescence, however. As seen from Fig. 1 there is clearly no relationship between the rate of appearance of this rearrangement product and the kinetic behavior of the colored species. Moreover, rigid degassing of the solutions led to appreciable diminishment of the color. We conclude that oxygen is involved in the production of an intermediate in these systems. However, this intermediate is kinetically unproductive in hydride transfer. Analogous formation of transient colors was not noted in the reaction of 2,6-di(substituted) compounds.

Substitution of the 2,4- and 6-position of a pyridinium salt dihydropyridine combination inhibits hydride exchange. Mixtures of **3c** and **4c** failed to undergo any detectable reaction up to 120° (highest temperature investigated). Likewise the 1,4-dihydropyridines **4d–g** with the analogous pyridinium salts **3d–g** were completely stable for extended periods at 120°. However, the 1,4-

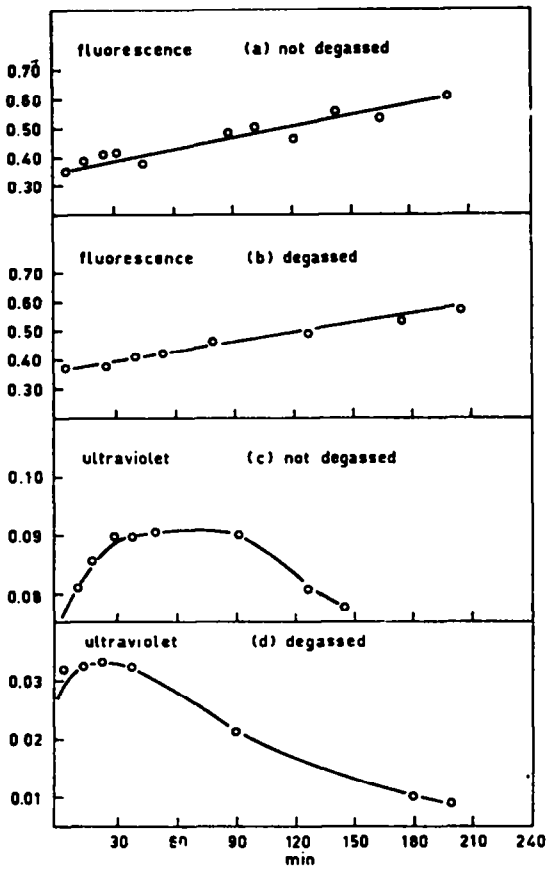


Fig. 1. Spectra taken in acetonitrile solution 6.5×10^{-3} M in 1,2-dihydropyridine and 3.5×10^{-2} M in pyridinium salt. Fluorescence spectra were obtained with an exciting wavelength of 388 nm and recorded at 460 nm. The UV spectra were measured at 500 nm.

dihydropyridines **4e–g** will donate hydride to less hindered pyridinium salts. When allowed to react with **3b** (bearing no Me groups) smooth hydride transfer to the 2- and 4-positions occurred. No attempt was made to determine the ratio **4b/5b** because of the rapid self-exchange that occurs at the fairly high temperatures used. Moreover, the 1,2-dihydropyridine isomers were not investigated as hydride donors. Only the rate of appearance of the pyridinium salts **4a–g** was followed.

Activation parameters were determined for a number of the reactions described here. The slope of the line is −0.99 consistent with a very mild accelerating effect by electron donating substituents. The term "4→4-transfer" refers to the "blind" process and "4→2-transfer" to the isomerization process. The values of $\Delta G^{\ddagger}_{25°}$, $\Delta H^{\ddagger}_{25°}$ and $T\Delta S^{\ddagger}_{25°}$ in the temperature range measured are compiled in the Table. A minimum of four points and usually five were used for each activation parameter determination. Duplicate runs were made. Usually the rates were followed by ^{1}H NMR spectroscopy using a temperature regulated probe. Sources of error in this method arise from the relatively high concentrations used (*ca* 0.3 M in 1,4-dihydropyridine), temperature fluctuations in the probe, lack of sensitivity in integration, and relatively narrow temperature range available owing to the method of observation. For **2,4b** the rates of the 4,4-exchange—with deuterium labeled compounds—were determined by ^{1}H NMR whereas the isomerization rate was determined by UV spectroscopy.

For the substituted derivatives **4d–g** the rate of hydride transfer to **3b** was determined and the relative rates have been correlated with σ_p constants. Electron donating groups are found to accelerate the rate of reaction modestly, $\rho = -0.99$.

DISCUSSION

There is precedent for compounds isoelectronic with (dihydro)pyridines (with regard to the aromatic system) for the hydride exchange reactions studied here. Pyridinium salts are both aromatic carbonium ions and iminium ions as emphasized in the resonance structures **6b,c**. The isoelectronic tropylium cation induces hydride scrambling in cycloheptatriene (eqn 10). Cyclo-

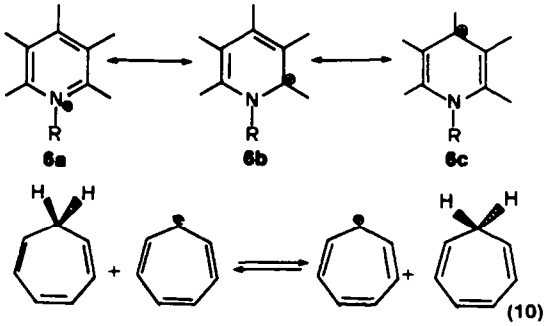


Table 1. Activation parameters for hydride exchange between dihydropyridines and pyridinium salts

Compound Set	Reaction	kcal/mole $\Delta G^{\ddagger}_{25°}$	$\Delta H^{\ddagger}_{25°}$	$\Delta T\ S^{\ddagger}_{25°}$
2a/4a	4,4-transfer	22.5	21.4	-1.1
"	4,2-transfer	23.1	16.9	-6.2
2b/4b	4,4-transfer	15.9	14.1	-1.8
"	4,2-transfer	14.9	11.9	-3.0
2a/4b	4,4+4,2-transfer	24.0	17.9	-6.1
2e/4b	"	26.4	22.5	-3.9

heptatriene donates hydride readily to a variety of carbonium ions and various carbonium ion promoted isomerizations of cycloheptatrienes are known.[14] That hydride transfer reactions also occur with dihydropyridine-pyridinium salt mixtures becomes understandable in the light of this knowledge.

The relatively low activation energies for hydride transfer and the sensitivity of exchange rate to steric effects is consistent with the reacting molecules being closely associated in the transition state. The entropy of activation term can determine the position of hydride acceptance as illustrated, for example, with the pyridine set 3-5a. Although $\Delta G^{\ddagger}_{25^\circ}$ for "blind" 4→4 exchange is lower than for 4→2 isomerization (22.5 compared to 23.1 kcal/mole) the $\Delta H^{\ddagger}_{25^\circ}$ for the "blind" exchange is actually much higher than for isomerization (21.4 compared to 16.9 kcal/mole). The rate compensation is found in the $T\Delta S^{\ddagger}_{25^\circ}$ contribution of −1.1 compared to −6.2 kcal/mole (Table 1).

It has recently been shown that the rate of hydride donation from dihydropyridines to various pyridinium salts and flavins parallels qualitatively the magnitude of the difference in redox potential.[5] In the examples reported here the overall energy change, at least in the "blind" reactions, is zero but the exchange reactions still proceed rapidly.

The simplest mechanistic model consistent with the present results is a concerted shift of hydride from the dihydropyridine to the pyridinium salt. For the case of 3-5b, the presence of an intermediate was demonstrated but this was revealed not be be a kinetically competent species. This is in contrast to recent results with nicotinamide systems wherein the presence of kinetically competent intermediates has been suggested.[15] However, a "concerted hydride shift" is by no means proved and there are many examples of hydride donation from dihydropyridines that appear to involve a series of one electron steps.[16]

The results described here have in our opinion considerable experimental consequences. In any reaction wherein an N-substituted 1,4-dihydropyridine donates a hydride to a substrate pyridinium salt will be generated and this will be capable of causing isomerization of the 1,4-dihydropyridine. If the substrate accepting hydride is only moderately reactive then only low conversions can be obtained owing to the autocatalytic isomerization caused by pyridinium salt. Owing to this problem the true reactivity of potential hydride acceptors may be underestimated.[17]

An equally serious problem, and one that cannot be ignored in the chemistry of NAD(P)H itself, is that the 1,2 (or 1,6 depending on symmetry) dihydro isomers could be hydride donors. Although the 1,2-dihydro isomer of 2a represents an energy pit into which hydride falls irreversibly, removal of the 2,6-Me groups (2b) causes the 1,2-isomer to become a hydride donor. Even more telling is that with N - benzyl - 1,4 - dihydronicotinamide, it has been shown recently that the N-benzylnicotinamide salt causes *reversible* transformation to the 1,6-isomer (eqn 12).[7] It is conceivable that similar complications occur with NAD(P)H itself.

EXPERIMENTAL

All m.ps were determined with a calibrated m.p. block or with a Mettler automatic m.p. apparatus. UV, IR, ^{1}H NMR, ^{13}C NMR, and mass spectra were obtained using common laboratory instruments.

Chemicals cited without reference were either in stock or were prepared following well-described procedures. Preparative methods and spectral data are given only for those (dihydro)pyridines that were previously unreported. Elemental analyses were carried out in the analytical laboratory of this university.

3,5 - *Di(ethoxycarbonyl)* - 1 - *methyl* - 2,6 - *di(trideuteriomethyl) pyridinium perchlorate* (3a') was prepared from the nondeuterated 3a (2.0 g, 5.4 mmole), which was refluxed for 2 hr in 4 ml EtOH–OD containing three drops of Et_3N. On cooling the pyridinium salt crystallized out and was removed by filtration. This procedure was repeated three times more. At this stage the protons of the 2,6-Me groups were 79% exchanged for D. To improve the D content the salt was refluxed 24 hr in 4 ml EtOH–OD containing Et_3N. The salt was isolated and thereafter subjected to the same treatment once more. After recrystallization there was obtained 1.26 g (3.4 mmole, 62%) of pyridinium perchlorate, m.p. 104–105.5°, containing at least 5.88 D atoms in the 2,6-Me groups as determined by ^{1}H NMR.

Preparation of 3,5 - *di(ethoxycarbonyl)* - 4 - *monodeuterio* - 2,6 - *di(trideuteriomethyl)* - 1,4 - *dihydropyridine* (4a'). The 3a' (475 mg, 1.27 mmole) was dissolved 7.5 ml D_2O saturated with $NaHCO_3$ (210 mg, 2.5 mmole). While stirring constantly $Na_2S_2O_4$ (1.65 g, 8.0 mmole) was added portionwise. After 2 hr stirring another 5 ml D_2O was added, stirring was continued 15 min and the ppt was then removed by filtration. There was obtained 328 mg (1.20 mmole, 95% yield) of crude 4a', which was recrystallized from 3 ml EtOD/H_2O (1:1) mixture to give pure 4a' (215 mg, 0.82 mmole, 65% yield), m.p. 83–85° (lit.[19] m.p. 86–87° for nondeuterated material).

Isomerization of 4a' *to the* 1,2-*dihydroisomer.* A sample of 4a' (160 mg, 0.61 mmol) was mixed with deuterated 3a' (10 mg, 0.039 mmole) in *ca.* 10 ml CD_3COCD_3. The mixture was refluxed for 43 hr. Extraction with water left *ca.* 150 mg material the ^{1}H NMR spectrum of which was identical with 5a save the absorptions for the 2,6-Me groups and 4-proton were missing.

3,5 - *Di(carbomethoxy)* - 1 - *trideuteriomethyl pyridinium perchlorate* (4b') was prepared starting from pyridine - 3,5 - dicarboxylate (8.4 g, 50.3 mmole), which as dry powder was allowed to react with $SOCl_2$ (68 g, 0.57 mole). The mixture was thereafter allowed to reflux for 3 hr after which time the solid had nearly completely gone into soln. The excess $SOCl_2$ was removed on the vacuum pump. To the residue chilled in an ice bath was added a mixture of MeOH (15 ml) and pyridine (0.15 mole). The mixture was allowed to come to room temp. The soln was made basic with sat Na_2CO_3 aq and the ppt formed was taken up in benzene. The benzene layer was dried; filtration and removal of solvent left crude diester (6.2 g, 31.8 mmole, 63% yield).

Under stirring and N_2 a soln of CD_3OD (1 ml) in 15 ml dry ether was treated with MeLi (16 ml of 5% soln in ether) at 0°. After standing 10 min *p*-toluenesulfonyl chloride (4.4 g, 23 mmole) dissolved in 15 ml dry ether was added dropwise and thereafter the mixture was stirred for 3 hr at room temp. The LiCl was removed on a glass filter; removal of the solvent left crude trideuteriomethyltosylate (4 g, 21.4 mmole, 93% yield based on sulfonyl chloride).

Crude trideuteriomethyltosylate (4 g) and crude 3,5 di(carbomethoxy)pyridine (3.7 g) were dissolved in dry acetonitrile (15 ml) and refluxed for 12 hr. The solvent was removed, the residue was dissolved in 10 ml water saturated with $NaClO_4$. After standing a ppt formed, which was removed by filtration, washed with a small amount of water, and recrystallized from 1:1 water–MeOH to give 4b' (2.2 g, 7.03 mmole, 35% yield based on pyridine).

Synthesis of 4-*phenyl substituted* 3,5 - *dimethoxycarbonyl*) - 1,4 *dihydropyridines* (4d–g) was carried out with a slight modification of the normal conditions for condensation. Methyl acetoacetate (11.6 g, 100 mmole) and benzaldehyde or substituted benzaldehyde were dissolved in MeOH (80 ml) in which ammonia (2.4 g, 140 mmole) had been dissolved. The mixture was slowly warmed to reflux and held at that temp for 15 hr. The mixture was cooled and half of the MeOH was removed. The ppt was collected on a filter and was washed with a small amount of cold

MeOH. Recrystallization from MeOH gave in 60–65% yield the crude 1,4-dihydropyridine, which after drying was used without further purification.

The dihydropyridine (60 mmole) was mixed intimately with sulfur (30 mmole). The mixture was heated in a metal bath to 180° for *ca.* 80 min until evolution of H_2S had essentially ceased. The residue was taken up in 4 N HCl (150 ml) and thereafter filtered. The filtrate was neutralized with Na_2CO_3 and thereafter extracted with ether. After drying over $MgSO_4$ and removal of solvent the pyridine was recrystallized from 80% MeOH:20% water; average yield 80%.

The pyridine (35 mmole) was dissolved in 100 ml dry CH_2Cl_2; methyl fluorosulfonate (45 mmole) was added by syringe to this soln (CAUTION: *methylfluorosulfonate must be handled as an extremely dangerous chemical*). After stirring for 2 hr MeOH was added to destroy the excess methyl fluorosulfonate. The solvent was removed, the residue was taken up in 50 ml MeOH and 10 ml sat $NaClO_4$ aq was added. After 2–3 hr stirring the pyridinium perchlorate was removed by filtration and recrystallized from 1:1 MeOH–H_2O, yield 65–70%.

The pyridinium salt (25 mmole) was suspended in 60 ml water. The suspension was held under N_2 and over 10 min $Na_2S_2O_4$ (10 g, 57 mmole) was added together with sufficient sat $NaHCO_3$ aq to maintain the pH at 7–8. This point is important: at low pH the dithionite decomposes and the pyridinium salt is demethylated; at higher pH the product 1,4-dihydropyridine is saponified. After 2 hr stirring at room temp. the soln was extracted with ether and the crude 1,4-dihydropyridine was recrystallized from MeOH, yield 10–20%. Data for the dihydropyridines **4d–g** follow:

4d (R = C_6H_5), overall yield 5.5%, m.p. 205–206°; IR (KBr) 1690, 1700 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 2.47 (broad s, 6, 2,6-CH_3), δ 3.7 (s, 6, OCH_3), δ 3.25 (s, 3, CH_3), δ 5.08 (broad s, 1, 4H), and δ 6.95–7.20 (complex 5, C_6H_5). (Found: C, 68.73; H, 6.74; N, 4.46. Calc. for $C_{18}H_{21}NO_4$: C, 68.56; H, 6.71; N, 4.44%).

4e, (R = 4-$CH_3OC_6H_4$), overall yield 2.5%; m.p. 162–163°; IR (KBr) 1695 cm^{-1} (C=O); ^1H NMR (CD_3COCD_3): δ 2.35 (s, 6, 2, 6-CH_3), δ 3.50 (s, 6, OCH_3), δ 3.15 (NCH_3), δ 4.97 (broad s, 1, 4-H), and δ 6.5–7.0 (complex, 4, C_6H_4). (Found: C, 65.98; H, 6.68; N, 4.04. Calc. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06%).

4f, R = 4-$CH_3C_6H_4$, overall yield 1.9%; m.p. 175.5–178°; IR (KBr) 1690, 1700 cm^{-1} (C=O); ^1H NMR (CD_3CN) δ 2.42 (broad s, 6, 2, 6-CH_3), δ 3.62 (broad s, 5, OCH_3), 3.17 (broad s, 3, NCH_3), δ 5.05 (s, 1, 4-H), and δ 7.05 (s, 4, C_6H_4). (Found: C, 69.08; H, 7.10; N, 4.22. Calc. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; H, 4.25%).

4g, R = 4-ClC_6H_4, overall yield 2.5%; m.p. 178.5–180.5°, IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR (CD_3CN): δ 2.40 (s, 6, 2,6-CH_3), δ 3.62 (broad s, 6, OCH_3), δ 3.17 (broad s, 3, NCH_3), δ 5.05 (s, 1, 4-H), and δ 7.15–7.20 (m, 5, C_6H_5). (Found: C, 61.51; H, 5.70; N, 3.96. Calc. for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.00).

Kinetic measurements. The isomerization of **3** and **5** was followed with the aid of UV measurements. Dihydropyridine (0.65 mmole) and pyridinium salt (0.065 mmole) were dissolved in 2 ml acetonitrile (Baker Reagent Crude, distilled from P_2O_5). The mixture was held in a water bath with a temp. control of ±0.1°. At appropriate time intervals a 0.100 ml sample was taken, which was diluted 250× with acetonitrile. The increase in absorption at 283.5 mm, which wavelength is used to follow the formation of **5c**, was measured on a Zeiss PMQ spectrophotometer.

Kinetic experiments followed by ^1H NMR spectroscopy were done on a JEOL 60 MHz apparatus provided with a variable temp. probe. The abs temp was measured using a MeOH correlation chart. In a typical isomerization experiment pyridinium salt (0.078 mmole) and dihydropyridine (0.77 mmole) were dissolved in 463 mg deuterioacetonitrile. For the case of **5d**, it was possible only to measure the total rate of conversion to **5b'** ("blind exchange") and **3b'** (1,4-dihydroisomer) by measuring the increase in the N–Me absorption at δ 4.45 for the pyridinium salt **4b**.

Note Added in Proof: Recently van Eikeren and Grier[18] have offered arguments that the exchange reaction between N-benzyl-1,4-dihydro-nicotinamide and its corresponding pyridinium chloride is not concerted. Neither the 1,2 nor the 1,6-dihydroisomers are implicated as intermediates, however.

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