$$[Rh(diphos)]^+ + >C{=}C< \overset{K_4}{\rightleftharpoons} [Rh(diphos)(>C{=}C<)]^+ \text{ (rapid equilibrium)} \quad (5)$$

$$[Rh(diphos)(>C{=}C<)]^+ + H_2 \xrightarrow{k_6} [Rh(diphos)]^+ + H{-}\overset{|}{C}{-}\overset{|}{C}{-}H \text{ (rate determining)} \quad (6)$$

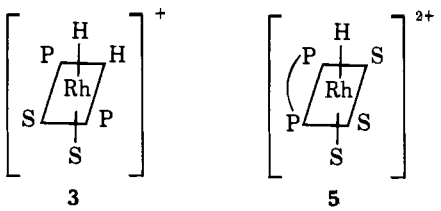
$$\frac{-d[>C{=}C<]}{dt} = \frac{k_6 K_4 [Rh_{tot}][>C{=}C<][H_2]}{1 + K_4[>C{=}C<]} \quad (7)$$

the spectrophotometric value (see above). Kinetic studies on other substrates are in progress.

It should be noted that our mechanism for the $[Rh(diphos)]^+$-catalyzed hydrogenation of alkenes departs significantly from that invoked for the corresponding $[Rh(PPh_3)_2]^+$-catalyzed reaction in which a principal pathway involves the hydrido complex, $[RhH_2(PPh_3)_2(solvent)_n]^+$.[7]

The different reactivities of $[Rh(diphos)(nor)]^+$ and $[Rh(PPh_3)_2(nor)]^+$ toward H_2, reflected in eq 1 and 2, are intriguing as well as being relevant to the mechanistic features of the catalytic hydrogenation reactions of the two species. A possible explanation of this difference is that, whereas $[Rh(PPh_3)_2]^+$ can form an H_2 adduct of structure **3** in which neither H ligand is trans to a phosphine ligand,[4,7] this is not possible (assuming cis disposition of the two H atoms) in the case of a chelating diphosphine ligand in which the two P atoms are constrained to being in mutually cis positions. This is expected to contribute to the instability of the H_2 adduct of $[Rh(diphos)]^+$ and to result in a considerably reduced equilibrium constant for the oxidative addition of H_2 to **2**, apparently to the point where the hydride cannot be detected. This reasoning suggests that $[Rh(diphos)]^+$ should, however, be capable of the facile oxidative addition of *one* hydrogen ligand, i.e., of H^+. In accord with this expectation, it was found that the addition of a noncoordinating acid such as HBF_4, HPF_6, or $HClO_4$ to a methanol or acetonitrile solution of $[Rh(diphos)]BF_4$, reversibly discharged the color of the $[Rh(diphos)]^+$ ion, the spectral changes being *quantitatively* identifiable with the reversible equilibrium of eq 8, with K_8 (MeOH) = 11 ± 2 M^{-1}. The ^1H NMR spectrum of $[HRh(diphos)]^{2+}$ in acetonitrile clearly revealed the hydride ligand coupled to the Rh atom and to two equivalent P atoms (δ −15.7 (J_{Rh-H} = 12.1 Hz, J_{P-H} = 17.2 Hz, also confirmed by ^{31}P NMR), in accord with structure **5**.

$$[Rh(diphos)]^+ + H^+ \overset{K_8}{\rightleftharpoons} [HRh(diphos)]^{2+} \quad (8)$$



3 **5**

These studies, some of which are still being elaborated, have revealed a number of previously unrecognized features of the coordination chemistry and catalytic activity of cationic rhodium complexes containing *chelating* diphosphine ligands which differ strikingly from the chemistry of the corresponding monodentate phosphine complexes. The chemistry of these complexes in relatively poorly coordinating solvents such as methanol, which are typically used for catalytic hydrogenation, appears to be dominated by their "ligand deficiency" as reflected in the formation of unusual polynuclear species such as $[Rh_2(diphos)_2]^{2+}$ and $[Rh_3(dipos)_3(OMe)_2]^+$, and in the strong binding of typically poor ligands such as arenes. It seems likely that the striking stereoselectivity which these catalysts exhibit in the asymmetric catalytic hydrogenation of prochiral olefins such as amidoacrylic and amidocinnamic acids reflects the strong tendency of the functional groups typically present in such substrates (C_6H_5, COOR, NHCOR, etc.) to "coordinate" to the Rh (as has been demonstrated in the comparison of styrene and 1-hexene) and thereby to exert a pronounced "orienting" influence. Our identification of reaction 5 opens up the opportunity for the direct systematic investigation of the effect of various substituents of olefinic substrates both on the equilibrium constants for the binding of the substrate (K_4) and on the structural features (potentially susceptible to elucidation both by NMR and by x-ray diffraction) of the resulting $[Rh(diphos)(>C{=}C<)]^+$ adducts which are key intermediates in the catalytic hydrogenation. Such investigations are in progress.

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(10) Crystal data of $[Rh_2(diphos)_2][BF_4]_2 \cdot CF_3CH_2OH$ (obtained by recrystallizing $[Rh_2(dlphos)_2][BF_4]_2$ from CF_3CH_2OH): space group P_{ccn}; a = 28.528 (7), b = 11.842 (3), c = 15.829 (5) Å; ρ_{obsd} = 1.57 vs. ρ_{calcd} = 1.585 for Z = 4. Data were collected on a Syntex P_{2_1} diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by MULTAN procedure and refined by full-matrix least-squares to R = 0.057, R_W = 0.089, using 3824 reflections with $F^2 \geq 3\sigma_{F^2}$ out of 4726 collected. The uncoordinated phenyl groups and lattice solvent molecule were treated as rigid bodies and the hydrogen atoms as fixed atom contributions at positions corresponding to normal geometries; anisotropic thermal parameters were used for the other atoms. Details of the refinement and structure to be published.
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Jack Halpern,* Dennis P. Riley
Albert S. C. Chan, Joseph J. Pluth
Department of Chemistry, The University of Chicago
Chicago, Illinois 60637
Received August 17, 1977

Models for NADH Coenzymes. Isotope Effects in the *N*-Benzyldihydronicotinamide/*N*-Benzylnicotinamide Salt Transhydrogenation Reaction

Sir:

The study of oxidation-reduction reactions of models for nicotinamide coenzymes has provided a great deal of information about the mechanism of such processes.[1] Perhaps the most fundamental redox reaction involving the dihydropyridine/pyridinium salt redox couple is the transhydrogenation reaction. An in-depth study of the transhydrogenation reaction has special appeal because of the symmetry between reactants

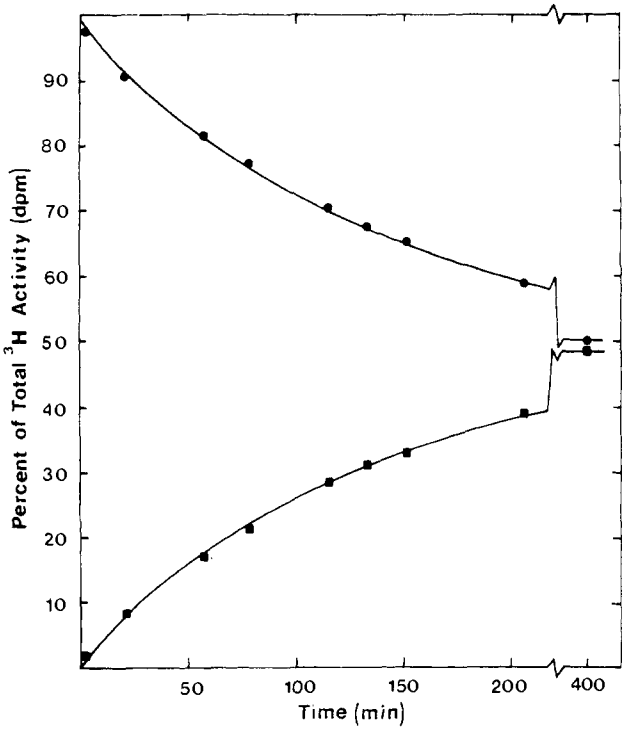
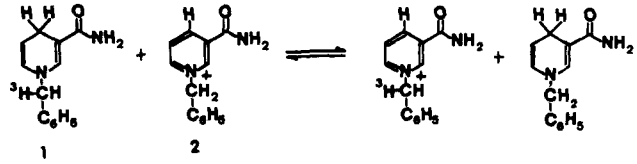


Figure 1. Time course of the *N*-benzyldihydronicotinamide (●)/*N*-benzylnicotinamide salt (■) transhydrogenase reaction in an acetonitrile—0.1 M borate (pH 8.8) buffer mixture (1:3 v:v) at 40.0 ± 0.1 °C. Initial conditions: 0.029 M *N*-[*benzyl*-^{3}H]-1,4-dihydronicotinamide and 0.031 M *N*-benzylnicotinamide chloride.

Scheme I



and products which greatly simplifies the mechanistic picture. In this communication, we wish to report on our studies of the *N*-benzyl-1,4-dihydronicotinamide/*N*-benzylnicotinamide chloride transhydrogenation reaction. We wish to report two major findings: (a) the measured secondary isotope effects during transhydrogenation are exactly *opposite* to those predicted by considering changes in hybridization at the 4 position in going to the transition state, and (b), although the evidence supports a multistep process, the 1,2- or 1,6-dihydropyridine may be excluded as an obligatory intermediate.

The course of the transhydrogenation reaction was monitored by using a radiochemically labeled dihydronicotinamide or nicotinamide salt and observing the change in the specific activity of the reaction components (Scheme I) as a function of time. In a typical experiment, pre-equilibrated buffered solutions of *N*-[*benzyl*-^{3}H]dihydronicotinamide[2a] and *N*-benzylnicotinamide chloride are mixed and maintained at 40.0 ± 0.1 °C. Aliquots are removed at various times and the components separated by a high pressure liquid chromatograph coupled to a UV detector. All peaks are individually collected and assayed for radioactivity by liquid scintillation counting. Observed counts per minute are corrected for quenching by the use of an external standard. We observe that the sum of the ^{3}H activity over all peaks remains constant during the course of the transhydrogenation reaction and is equal to the total ^{3}H activity injected into the chromatograph. Furthermore, the peaks corresponding to *N*-benzyldihydronicotinamide and *N*-benzylnicotinamide salt account for >97% of the total ^{3}H activity during 3 half-lives of transhydrogenation. The progress

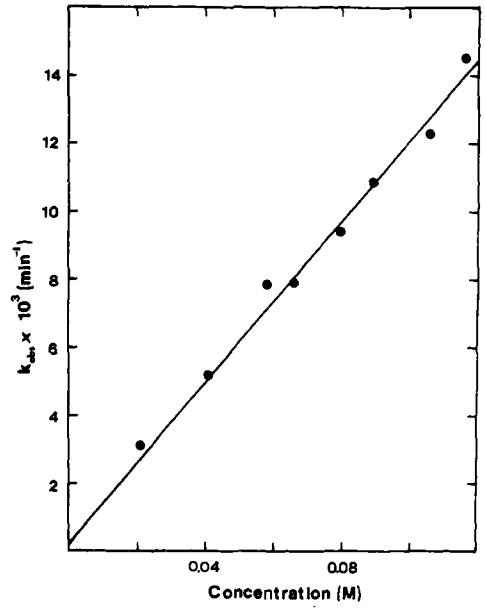


Figure 2. Variation of observed first-order rate constant of transhydrogenation (k_{obsd}) as a function of the sum of the dihydronicotinamide and nicotinamide salt concentrations. Reactions were carried out in acetonitrile–0.1 M phosphate (pH 8.6) buffer mixture (1:3 v:v) at 40.0 ± 0.1 °C.

of the transhydrogenation reaction is evaluated by observing the percent of the total ^{3}H activity of each component as a function of time.[2b] A typical run is shown in Figure 1.

In principle, the transhydrogenation reaction is an example of a simple isotope exchange reaction.

$$A^* + B \rightleftharpoons A + B^* \quad (1)$$

Although such reactions represent second-order processes, their kinetic behavior are first order as a result of a constant concentration term.[3] Furthermore, such reactions can be shown to fit the following mathematical scheme

$$\ln (B^*_\infty - B^*_t) = -k_2(A^*_0 + B_0)t + \ln (B^*_\infty - B_0) \quad (2)$$

where k_2 is the second-order rate constant and the subscripts t, 0, and ∞ correspond to the conditions at a given time, at the beginning of the reaction, and at infinity, respectively. The relevance of the above scheme to the transhydrogenation reaction is demonstrated in the following experiment. Using *N*-benzyl-[7-^{14}C]nicotinamide chloride, the appearance of ^{14}C activity in the *N*-benzyldihydronicotinamide component follows first-order kinetics for more than 4 half-lives. Moreover, the variation of the observed first-order rate constant, k_{obsd}, as a function of the *sum* of the concentration of *N*-benzyldihydronicotinamide and *N*-benzylnicotinamide chloride is linear (Figure 2). The slope of 0.119 ± 0.003 L/mol^{-1} min^{-1} represents the second-order rate constant of transhydrogenation at the indicated conditions.

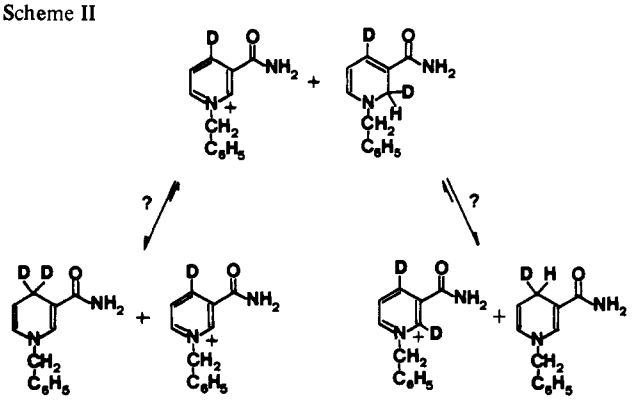
One possible mechanistic pathway for the transhydrogenation reaction requires that the isomeric 1,2- or 1,6-dihydronicotinamide be an obligatory intermediate in the reaction. The interconversion of 1,4-dihydropyridines to their isomeric species has been the subject of several reports.[4] We have tested this hypothesis by synthesizing *N*-benzyl-4,4-dideuteriodihydronicotinamide and *N*-benzyl-4-deuterionicotinamide chloride and examining the deuterium content at the 4 position before and after transhydrogenation. If the 1,2- or 1,6-dihydronicotinamide was an obligatory intermediate (Scheme II), the deuterium label would be scrambled after transhydrogenation. NMR examination of the reaction components after >4 half-lives of transhydrogenation indicated that 97 ± 2% of the deuterium is retained in the original 4 position. This

Table I. Isotope Effects for the *N*-Benzyl-1,4-dihydronicotinamide/*N*-Benzylnicotinamide Salt Transhydrogenation Reaction[a]

Reaction	1,4-Dihydronicotinamide (**1**)	Nicotinamide chloride salt (**2**)	Kinetic ratio[b]	Isotope effect[c]	Notes[d]
A	*N*-Benzyl-[7-^{14}C]- (**1a**) *N*-[*benzyl*-^{3}H]- (**1b**)	*N*-Benzyl- (**2c**)	1.00 ± 0.01 0.95 ± 0.02	0.99 ± 0.02	Control[e] ($sp^3 \rightarrow sp^2$)
B	*N*-Benzyl- (**1c**)	*N*-Benzyl-[7-^{14}C]- (**2a**) *N*-[*benzyl*-^{3}H]- (**2b**)	1.05 ± 0.03 0.93 ± 0.07	1.03 ± 0.07	Control[e] ($sp^2 \rightarrow sp^3$)
C	*N*-Benzyl-[7-^{14}C]- (**1a**) *N*-Benzyl-[4-^{3}H]- (**1d**)	*N*-Benzyl- (**2c**)	1.58 ± 0.02 1.67 ± 0.14	0.79 ± 0.02[f]	Secondary tritium ($sp^3 \rightarrow sp^2$)
D	*N*-Benzyl- (**1c**)	*N*-Benzyl-[7-^{14}C]- (**2a**) *N*-Benzyl-[4-^{3}H]- (**2d**)	1.39 ± 0.05 1.16 ± 0.07 1.24 ± 0.07	1.30 ± 0.12	Secondary tritium ($sp^2 \rightarrow sp^3$)
E	*N*-Benzyl-[7-^{14}C]- (**1a**) *N*-[*benzyl*-^{3}H]-[4-^{2}H]- (**1e**)	*N*-Benzyl- (**2c**)	1.51 ± 0.07 1.46 ± 0.10	6.2 ± 2.0[g]	Primary deuterium ($sp^3 \rightarrow sp^2$)

[a] At 40.0 ± 0.1 °C in acetonitrile–0.1 M aqueous sodium borate buffer (pH 8.8) mixture (1:3 v:v); all kinetic runs were carried out at a concentration of ~0.02 M in each reactant. [b] The ratios of the specific rates of the two isotopically labeled nicotinamides [$k(^{14}C)/k(^{3}H)$] were obtained from the fractional conversion of the two isotopic nicotinamides to their conjugate species as described in text (kinetic ratio = $[^{3}H/^{14}C]_0[^{14}C/^{3}H]_t$); the errors represent the standard deviation of the intercept of the least-squares best-fit line of the observed kinetic ratio as a function of time for each experiment. [c] Isotope effects calculated from kinetic ratios corrected for multiple pathways by eq 5 and 6; represents the weighted mean of two or more kinetic runs.[14] [d] Hybridization change at the 4 position incurred by the labeled species is given in parenthesis. [e] Control reactions involve transhydrogenation of nicotinamide species labeled with tritium at nontransferable positions. [f] Calculated from the kinetic ratio using eq 4. [g] Calculated from the kinetic ratio using eq 6 and the assumption that $s_T = (S_D)^{1.442}$; S_D = 0.85 ± 0.02.

Scheme II



demonstrates that the transhydrogenation reaction results from the specific transfer of a hydrogen from the 4 position of the dihydronicotinamide to the 4 position of the nicotinamide salt. Moreover, this result assures that nicotinamides, isotopically labeled at the 4 position, will not undergo label scrambling during the kinetic isotope effect studies discussed below.

The measurement of the secondary isotope effects during the transhydrogenation reaction (Table I) provides anomalous secondary isotope effects. Isotope effects were calculated from the measured competition reaction between two isotopically labeled nicotinamides and their conjugate redox species.[5] For example, a solution of *N*-benzyl-[4-^{3}H]dihydronicotinamide and *N*-benzyl-[7-^{14}C]dihydronicotinamide was reacted with a solution of unlabeled *N*-benzylnicotinamide chloride in a buffered solvent mixture (reaction C on Table I). During the course of the transhydrogenation reaction (always <20% completion) aliquots were removed and injected into the HPLC system, and the components assayed for ^{3}H and ^{14}C activity. The ratio of the specific rates of the two dihydronicotinamides (kinetic ratio) was obtained from the observed fractional conversion of the two radiochemically labeled dihydronicotinamides to their corresponding labeled nicotinamide salts through the following equation:

$$(\text{kinetic ratio})_t = [(^{3}H/^{14}C)(\mathbf{1})]_0[(^{14}C/^{3}H)(\mathbf{2})]_t \quad (3)$$

Kinetic ratios were corrected for any back-reaction by determining the kinetic ratio at the very beginning of transhydrogenation. The latter was obtained from the intercept of a plot of the kinetic ratio as a function of time.

Scheme III

$$\mathbf{1a} + \mathbf{2c} \xrightarrow{2k_H} \mathbf{2a} + \mathbf{1c}$$

$$\mathbf{1d} + \mathbf{2c} \begin{cases} \xrightarrow{k_H'} \mathbf{2d} + \mathbf{1c} \\ \rightarrow \mathbf{2c} + \mathbf{1d} \end{cases}$$

kinetic ratio (reaction C) = $2k_H/k_H'$

"identity transfer"

To assure that the procedure for the simultaneous assay of ^{3}H and ^{14}C activity was unbiased, the kinetic ratios of two control reactions (reactions A and B in Table I) were measured. Since the radiochemical labels were located some distance from the transferable hydrogen, no isotope effect was expected and a kinetic ratio of 1 may be predicted. The excellent agreement between the observed and predicted kinetic ratios provides strong support for the accuracy of the procedure.

Substitution of tritium or deuterium on a carbon which changes from sp^3 to sp^2 hybridization in the rate-determining step of a reaction produces a secondary kinetic isotope effect[6] of 20 and 15%, respectively; i.e., $k_H/k_T \simeq 1.2$. Substitution of tritium or deuterium on a carbon undergoing a hybridization change in the reverse direction, from sp^2 to sp^3, produces a secondary kinetic isotope effect of about the same magnitude but in the inverse direction; i.e., $k_H/k_T \simeq 0.83$. If the mechanism of transhydrogenation involves a simple hydride transfer

Scheme IV

$$\mathbf{1c} + \mathbf{2a} \xrightarrow{2k_H} \mathbf{2c} + \mathbf{1a}$$

kinetic ratio (reaction D) = k_H/k_H''

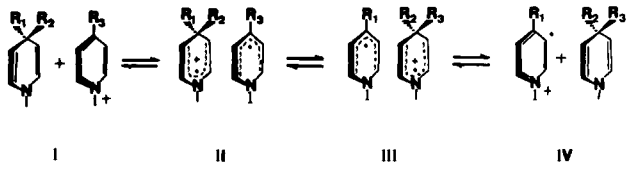
$$\mathbf{1c} + \mathbf{2d} \xrightarrow{2k_H''} \mathbf{2c} + \mathbf{1d}$$

(Schemes III and IV) we can relate the measured kinetic ratios and the secondary tritium isotope effects (S_T) by the following equations:

$$S_T(sp^3 \rightarrow sp^2) = k_H/k_H' = \tfrac{1}{2}[\text{kinetic ratio (reaction C)}] \quad (4)$$

$$S_T(sp^2 \rightarrow sp^3) = k_H/k_H'' = [\text{kinetic ratio (reaction D)}] \quad (5)$$

Scheme V



I II III IV

The results, as given in Table I, show that the logical predictions about the magnitudes of the isotope effects are incorrect; namely, the secondary isotope effects are opposite to the predictions based on hybridization changes. The internal consistency of the results is demonstrated by the fact that the measured secondary isotope effects are, within experimental error, mathematical inverses of each other as expected for the symmetrical transhydrogenation reaction.

The primary deuterium isotope effect can be calculated from the data of reaction E by the following equation[1f]

$$P_D = \frac{[\text{kinetic ratio (reaction E)}]}{2 - [\text{kinetic ratio (reaction E)}]/S_D} \quad (6)$$

where S_D represents the secondary deuterium isotope effect. The latter may be calculated from the secondary tritium isotope effect by the following relation:[7]

$$1.442 = \ln (S_T)/\ln (S_D) \quad (7)$$

The results of these calculations are given in Table I.

We propose the mechanism shown in Scheme V as the minimum mechanism needed to rationalize the data. A simple hydride-transfer mechanism is not consistent with the anomolous secondary isotope effects and the results of some preliminary experiments discussed below. Owing to the symmetry between reactants and products, the free-energy profile of the transhydrogenation reaction should be symmetric. This implies that any postulated first step in the mechanism must be identical with the last step. On this basis, a mechanism which involves initial electron transfer followed by hydrogen atom transfer may be eliminated. A remaining possibility consistent with the symmetry of the reaction (Scheme V) involves initial electron transfer followed by proton transfer and another electron transfer.

The proposed formation of the radical cation through a single electron transfer has precedents in the chemistry of dihdropyridines[8] and related flavins.[9] In addition, preliminary transhydrogenation experiments under different buffer conditions show the formation of substantial quantities of the primary hydration product of *N*-benzyldihydronicotinamide.[10] The rate of formation of the latter is first order in dihydropyridine and first order in nicotinamide salt. In the absence of the nicotinamide salt, the hydrolysis product is not observed. Furthermore, product studies of closely related redox systems indicate the appearance of substantial amounts of radical coupling products.[11] The observed primary isotope effect (R_1 = H; R_2 = ^{2}H; R_3 = H) of 6.2 indicates that C-H bond breakage is occurring in the rate-determining step.[12] The magnitude is consistent with a proton-transfer step.

Secondary kinetic isotope effects reflect a net change in the bond force constants at the isotopically substituted atom between the ground state and the transition state. Hence, normal secondary isotope effects ($k_H/k_D > 1$) arise from a decrease in the force constant, and, conversely, inverse secondary isotope effects arise from an increase in the bond force constant in going from the ground state to the transition state. From symmetry considerations, the rate-determining transition states in reactions C (R_1 = ^{3}H; R_2 = H; R_3 = H) and D (R_1 = H; R_2 = H; R_3 = ^{3}H) must be identical. Furthermore, the hybridization at the 4 position in the rate-determining step is exactly between sp^3 and sp^2. Since the hybridization change is small, one would expect step II $\rightleftharpoons$ III in Scheme V to be a minor contributor to the observed secondary isotope effect. The substitution of deuterium or tritium at the 4 position of the dihydropyridine should increase the equilibrium constant for the first step (I $\rightarrow$ II) since the intermediate radical cation (II) is stabilized by the apparent electron-supplying effect of deuterium or tritium relative to hydrogen.[6] Hence, the changes in bond force constants occurring at the isotopically substituted 4 position during the course of the reaction result from minor contributions due to changes in hybridization (normal isotope effects) and major contributions due to inductive effects on the radical cation (inverse isotope effects).

Although secondary isotope effects in dihydronicotinamide reductions have never been measured, several authors have used a value of 1.0 as an assumption in their calculation of primary isotope effects.[1d-f] If the results reported here can be extended to the reactions of dihydronicotinamides with other oxidizing agents, the calculated values of the primary isotope effects determined kinetically by these authors are low. Moreover, calculated values of isotope effects in NADH dependent enzyme reactions have also assumed a value of 1 for the secondary isotope effects and thus the reported values of primary isotope effects probably represent low estimates.[13] An investigation to determine the significance of secondary isotope effects in dihydronicotinamide reductions with other oxidizing agents is in progress.

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Paul van Eikeren,* David L. Grier
Department of Chemistry, Harvey Mudd College
Claremont, California 91711
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