when M = Pt and 166.8° when M = Pd, whereas the corresponding terminal carbonyl groups show an average angle of 177.7 and 175.8°, respectively.
(9) Cotton, F. A. *Prog. Inorg. Chem.* **1977**, *21*, 1–28.
(10) In the related $Sn[Fe_2(CO)_8]_2$ derivative, the shortest Sn·C contacts are longer than 3.0 Å.[11]
(11) Lindley, P. F.; Woodward, P. *J. Chem. Soc. A* **1967**, 382–392.
(12) Chini, P.; Ciani, G.; Garlaschelli, L.; Manassero, M.; Martinengo, S.; Sironi, A.; Canziani, F. *J. Organomet. Chem.* **1978**, *152*, C35–C38.
(13) This difference in charge distribution in the $[Fe_4M(CO)_{16}]^{2-}$ (M = Pd, Pt) dianions is in agreement with Pauling electronegativities of the metals. Electron transfer from iron to platinum has been previously inferred from Mossbauer isomer shift in Fe–Pt Alloys.[14]
(14) Vannice, M. A.; Garten, R. L. *J. Mol. Catal.* **1975–1976**, *1*, 201–222.
(15) Longoni, G.; Chini, P. *J. Am. Chem. Soc.* **1976**, *98*, 7225–7231, and references therein.
(16) Hultgren, R.; Zapffe, C. A. *Zeit. Krist.*, **1938**, *99*, 511.
(17) Comparable values are 2.75 Å for palladium metal, 2.582 Å for $Mo_2Pd_2Cp_2(CO)_6(PEt_3)_2$,[18] and 2.89 Å for the $PdH_{0.7}$ phase.[19]
(18) Bender, R.; Braunstein, P.; Dusasoy, Y.; Protas, J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 596–597.
(19) MacKay, K. M. In "Comprehensive Inorganic Chemistry"; Pergamon: London, 1973; Vol. 1, p 23.
(20) Broach, R. W.; Dahl, L. F.; Longoni, G.; Chini, P.; Schultz, A. J.; Williams, J. M. *Adv. Chem. Ser.* **1978**, No. 167, 93–110.

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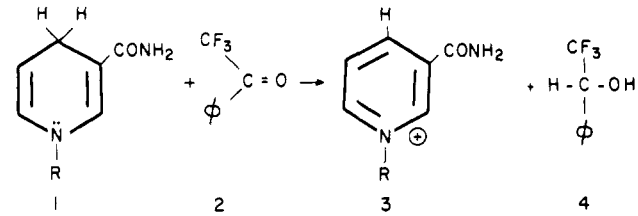
Models for Nicotinamide Coenzymes. Isotope Effect Discrepancies in the Reaction of Dihydronicotinamides with Trifluoroacetophenone Are Due to Adduct Formation

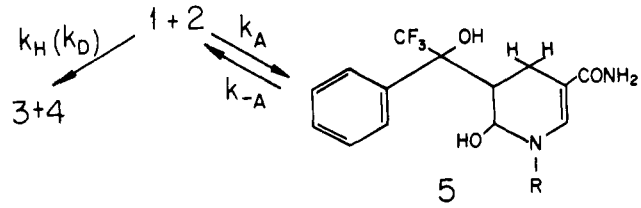
Sir:

Several years ago we suggested that the oxidation–reduction reaction of a 1,4-dihydronicotinamide (**1**) with trifluoroacetophenone (**2**) (Scheme I) proceeds via an intermediate.[1] This was based on our observation that isotope effects determined by comparison of the rates of disappearance of protio- and 4-deuteriodihydronicotinamides (**1** and **1**-d_1)[2] were small compared with those determined from the partitioning of hydrogen and deuterium from **1**-d_1 into the product phenyltrifluoroethanol (**4**). This discrepancy would be explained if there was a noncovalent intermediate on the reaction pathway, with the rate-determining step *preceding* the hydrogen transfer. Similar results were subsequently reported for other oxidations of dihydronicotinamides, and two-step mechanisms proposed for these reactions as well.[3] It now appears, however, that our conclusions were premature. In this report we demonstrate that the discrepancy in isotope effects is due to the reversible formation of a covalent adduct[4] **5** which is *not* on the pathway for the oxidation–reduction reaction (Scheme II).

Scheme I



Scheme II



The isotope effects were remeasured for two dihydronicotinamides under conditions minimizing the complicating unimolecular (hydration) component[1] in the disappearance of **1**. In 0.1 M $NaHCO_3$–0.1 M Na_2CO_3 buffer, pH 9.9, in 25% 2-propanol at 50 °C, the disappearance of **1** (UV, 355 nm) in the presence of a large excess of **2** is pseudo first order, with $k_{obsd} = k_{app}[\mathbf{2}]$. The initial rates of disappearance of dihydronicotinamides[2,5] **1**, **1**-d_1, and **1**-d_2 were measured simultaneously in identical solutions of **2** so as to determine the relative rates (k_{HH}/k_{HD}, k_{HH}/k_{DD}; Table I, entries 2 and 3) with maximum accuracy. The relative rates of transfer of H and D from **1**-d_1 to **2**, k_H/k_D, were determined in the above medium by isotopic analysis of the product alcohol **4** (Table I, entry 4). Data were corrected for the isotopic compositions of the samples of **1** used.[6] To make certain that deuterium had not been lost by exchange with solvent, the reactions were repeated with $[^3H]$-H_2O in the medium and **4** isolated as the *p*-nitrobenzyl ester.[1b] Scintillation counting of the ester showed that <0.1% of the hydrogen on the carbinol carbon (H–C–O) of **4** was derived from the solvent. The data confirm our report of discrepancies in isotope effects.

We must now consider this data in the light of formation of **5**. The adduct **5a** (R = propyl) precipitated in 10–15% yield when a buffered (0.1 M carbonate, pH 9.9) solution *saturated* in **1a** and **2** was held at 40 °C and was shown to have the IR,

Table I. Kinetic and Isotope Effect Data for Reactions of Dihydronicotinamides **1** with Trifluoroacetophenone (**2**)[a]

entry		dihydronicotinamide (R) **1a** (*n*-propyl)	**1b** (benzyl)
1	k_{app}, M^{-1} min^{-1} [b]	0.207 ± 0.014[c]	0.065 ± 0.003[d]
2	k_{HH}/k_{HD} (rel rate)[b,e,f]	1.29 ± 0.04[c]	1.55 ± 0.15[d]
3	k_{HH}/k_{DD} (rel rate)[b,e,g]	1.93 ± 0.13[c]	2.19 ± 0.11[d]
4	k_H/k_D (product analysis)[e,h]	6.7 ± 1.8	6.6 ± 1.7
5	$2k_H/(2k_H + k_A)$ (calcd, eq 3)	0.57 ± 0.06	0.64 ± 0.05
6	$2k_H/(2k_H + k_A)$ (calcd, eq 4)	0.53 ± 0.07	0.84 ± 0.14
7	k_H, M^{-1} min^{-1} }	0.06	0.02
8	k_A, M^{-1} min^{-1} } constants for Scheme II[i]	0.09	0.02
9	k_{-A}, min^{-1} }	0.006	0.005

[a] All measurements were done at 50.0 ± 0.2 °C in 0.1 M $NaHCO_3$–0.1 M Na_2CO_3 buffer, pH 9.9, ionic strength 0.5, in 25% 2-propanol (v/v). [b] Disappearance of **1** followed spectrophotometrically at 355 nm. [c] Average from 21 experiments over the range of [**2**] from 0.025 to 0.2 M. [d] Average from 11 experiments, [**2**] = 0.05–0.2 M. [e] Corrected for isotopic composition of starting samples of **1**. [f] Relative k_{app} for **1** and **1**-d_1. [g] Relative k_{app} for **1** and **1**-d_2. [h] 0.01 M **1**-d_1 and 0.04 M **2** were incubated for 48 h (>95% completion); crude **4** was isolated and analyzed by mass spectroscopy (average from three experiments). [i] k_H and k_A were calculated from the ratio $2k_H/(2k_H + k_A)$ and the assumption that $2k_H + k_A = k_{app}$. k_{-A} was chosen to fit data for **4** formation (e.g., Figure 2).

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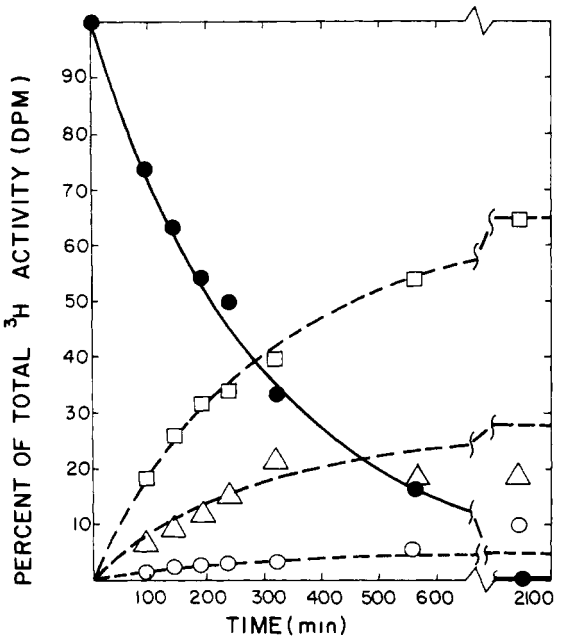

Figure 1. Time course of reaction of 0.01 M *N*-([^{3}H]benzyl)dihydronicotinamide (**1**) (●) and 0.08 M trifluoroacetophenone (**2**) at 40.0 ± 0.1 °C in 0.1 M borate buffer (pH 8.8)–acetonitrile (1:5 v/v). Products detected (by LC) are **3**, *N*-([^{3}H]benzyl)nicotinamide salt (□); two isomers of adduct **5** (sum given, △); and the primary hydration product of **1** (○). Curves calculated for the second-order reaction of **1** and **2**, k = 0.043 M^{-1} min^{-1}, in competing processes, ignoring decomposition of **5**.

NMR, and UV spectra expected for the assigned structure. Analogous adducts have been reported for several other aldehydes and ketones.[4,7]

If the formation of the adduct **5** *competes* with the redox process (Scheme II), the relative rates of disappearance of **1**, **1**-d_1, and **1**-d_2 will be given by

$$k_{HH}/k_{DD} = (2k_H + k_A)/(2k_D + k_A) \quad (1)$$

$$k_{HH}/k_{HD} = (2k_H + k_A)/(k_H + k_D + k_A) \quad (2)$$

These equations take into account the fact that either hydrogen at C-4 on **1** can be transferred, and assume a primary isotope effect but no secondary effects.[8] It is clear from them that the isotope effects k_H/k_D will be partially masked by the competing process k_A. If this is the only cause of the observed discrepancies, we can calculate the relative contribution of the redox reaction to the disappearance of **1** from

$$2k_H/(2k_H + k_A) = (1 - k_{DD}/k_{HH})/(1 - k_D/k_H) \quad (3)$$

$$2k_H/(2k_H + k_A) = [2(1 - k_{HD}/k_{HH})]/(1 - k_D/k_H) \quad (4)$$

(derived by rearranging eq 1 and 2, respectively).[4] The results (Table I, entries 5 and 6) imply that a significant fraction of the starting materials disappears initially by the alternative process of adduct formation.

This conclusion was tested by following the reaction of *N*-([^{3}H]benzyl)dihydronicotinamide (**1b**) and **2** by LC. Peaks detected by UV were collected and analyzed by liquid scintillation counting. Figure 1 shows the results of a typical experiment (at 40.0 °C, buffered acetonitrile–water, pH 8.8). The disappearance of **1b** follows the expected second-order kinetics (k_{app} = 0.043 M^{-1} min^{-1}). However, three radioactive products in addition to the nicotinamide salt **3b** are observed: the cis and trans isomers of adduct **5b** and the primary hydration product. The initial rates of formation of **3b** and **5b** are ~65 and 28%, respectively, of the rate of disappearance of **1b**, as predicted in entry 5 of Table I.

To demonstrate that the discrepancy between isotope effects from partitioning and from kinetics can be accounted for

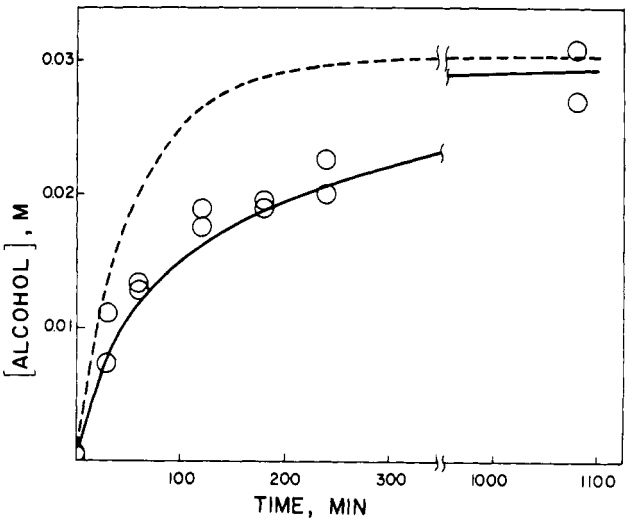

Figure 2. Appearance of phenyltrifluoroethanol (**4**) in reaction of propyldihydronicotinamide (**1a**, 0.030 M) with **2** (0.10 M), at 50 °C, pH 9.9, in 25% 2-propanol. Circles, experimental points (two reaction mixtures) from GLC analysis. Dashed line, calculated for bimolecular reaction, k_{app} = 0.207 M^{-1} min^{-1}. Solid line calculated for Scheme II, k_H = 0.06 M^{-1} min^{-1}, k_A = 0.09 M^{-1} min^{-1}, k_{-A} = 0.006 min^{-1}.

quantitatively by Scheme II, we studied the formation of phenyltrifluoroethanol (**4**) under conditions identical with those used for the isotope effect measurements (see footnote *a*, Table I). Figure 2 shows the results of an experiment with propyldihydronicotinamide (**1a**). The dashed line, which clearly does not fit the data, represents the concentration of **4** expected if the disappearance of **1** and **2** with the bimolecular rate constant k_{app} (from spectrophotometric experiments) yielded only **3** and **4**. The solid line represents the course of the reaction expected from Scheme II. In this case, the formation of **4** is the sum of two processes, one the direct reaction of starting materials and the other the reaction of **1** and **2** derived from slow dissociation of the adduct.[10] The values of k_H and k_A used to produce the calculated curve were based on the values of $2k_H/(2k_H + k_A)$ and $k_{app} = 2k_H + k_A$ from the isotope effects and spectrophotometric kinetics (Table I, entries 5 and 1, respectively). The values of k_{-A} were chosen for the best fit of the data, and could not reliably be determined to within better than a factor of 2. It is remarkable, though, that, if we assume the ratio $2k_H/(2k_H + k_A)$ to be very different (±>0.1) from that derived from the isotope effects, the fit to the data is much poorer. Similar results were obtained with benzyldihydronicotinamide (**1b**). This agreement between totally unrelated experimental approaches is very satisfying.

Note that Scheme II predicts that the disappearance of dihydronicotinamide **1** in the presence of excess **2** should also be the sum of two exponential decay processes. However, the relative contributions of the two processes in this case would be different from their contributions to the appearance of the alcohol, and the biphasic nature of the kinetics much less noticeable. Simulation of the kinetics of disappearance of **1a** in the presence of 0.1 M **2**, using Scheme II and the constants of Table I, shows that a semilog plot over 2 half-lives would appear essentially linear (r = 0.9990).

An independent determination of the isotope effect in the redox reaction was provided by double-labeling competition experiments. The reaction of a mixture of *N*-([7-^{14}C]benzyl)- and *N*-([^{3}H]benzyl)[4-^{2}H]dihydronicotinamides with **2** in acetonitrile–0.1 M borate (pH 8.8) (14:86 v/v) was analyzed by LC as previously described.[9a] The initial relative fractional conversions of the labeled **1b** and **1b**-d_1 into **3b** indicated[9a] a kinetic ratio of 1.68 ± 0.07 (two experiments). This is equiv-

alent (assuming insignificant secondary effects[8]) to a primary isotope effect, $k_H/k_D = 5.3 \pm 1.4$, in good agreement with partitioning experiments.

All of the data reported here can be accounted for by the reversible formation of the adduct **5** between the dihydronicotinamide and the ketone, which is *not* on the pathway for the oxidation-reduction reaction. Evidence concerning the redox reaction itself is consistent with a simple hydride transfer ($k_H/k_D \sim 6$, considerable transfer of charge at the transition state[1b]). Discrepancies between isotope effects determined by kinetics and by partitioning experiments are thus *not* valid evidence for an intermediate on the path to hydrogen transfer in this reaction, and we must question the significance of such evidence in the case of other reactions of dihydronicotinamides[3] as well. Indeed, under conditions where formation of hydrated, neutral adducts like **5** is unlikely (because of solvent composition or steric effects[4]), agreement between isotope effects measured by the two methods has been observed.[11] However, although we have now discounted some of the evidence which has supported proposals for intermediates (cation radicals?) in the redox reactions of dihydronicotinamides, other evidence for complex mechanisms in such processes remains.[12]

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References and Notes

(1) (a) Steffens, J. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 6694–6696. (b) Steffens, J. J. Ph.D. Thesis, Massachusetts Institute of Technology, 1971.
(2) **1**-d_1: *N*-alkyl[4-^{2}H]-1,4-dihydronicotinamide. **1**-d_2: *N*-alkyl-[4,4-^{2}H,^{2}H]-1,4-dihydronicotinamide.
(3) (a) Creighton, D. J.; Hajdu, J.; Mooser, G.; Sigman, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 6855–6857. (b) Creighton, D. J.; Hajdu, J.; Sigman, D. S. *Ibid.* **1976**, *98*, 4619–4625. (c) Shinkai, S.; Ide, T.; Hamade, H.; Manabe, O.; Kunitake, T. *J. Chem. Soc., Chem. Commun.* **1977**, 848–849.
(4) van Eikeren, P.; Grier, D. L.; Eliason, J. *J. Am. Chem. Soc.*, in press.
(5) **1**-d_2 was prepared by several cycles of reduction in D_2O and reoxidation, by the method of Caughey, W. S.; Schellenberg, K. *J. Org. Chem.* **1966**, *31*, 1978.
(6) Isotopic compositions of dihydronicotinamides were determined by NMR and mass spectrometry at low ionization voltage.
(7) Tagaki, W.; Sakai, H.; Yano, Y.; Ozeki, K.; Shimizu, Y. *Tetrahedron Lett.* **1976**, 2541–2544.
(8) Secondary α-deuterium isotope effects directly measured for such reactions[9] imply k_H/k_D(secondary) = 0.85–1.20. Such effects would alter the ratios calculated here by less than the experimental error.
(9) (a) van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 8057. (b) Kurz, L.; Frieden, C. *Biochemistry* **1977**, *16*, 5207–5216. (c) Colter, A. K.; Saito, G.; Sharom, F. J.; Long, A. P. *J. Am. Chem. Soc.* **1976**, *98*, 7833–7835.
(10) The kinetics for this scheme are characterized by two exponential decay processes, λ_1 and λ_2, the roots of $\lambda^2 + \lambda[(2k_H + k_A)[2] + k_{-A}] + 2k_Hk_{-A}[2] = 0$. Since **2** was not in large enough excess for a simple sum of exponentials to characterize the system exactly, numerical integration of the differential equations characterizing Scheme II was used: De Tar, D. F.; De Tar, C. E. *J. Phys. Chem.* **1966**, *70*, 3842–3847).
(11) (a) Dittmer, D. C.; Lombardo, A.; Batzold, F. H.; Greene, C. S. *J. Org. Chem.* **1976**, *41*, 2976–2981. (b) Kurz, L.; Frieden, C., private communication. (c) Ohno, A.; Yasui, S.; Yamamoto, H.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 294–296. (d) Ohno, A.; Yamamoto, H.; Okamoto, T.; Oka, S.; Ohnishi, Y. *Chem. Lett.* **1978**, 65–68.
(12) Kosower, E. M. *Prog. Phys. Org. Chem.* **1969**, *3*, 81–163. (b) Ohno, A.; Kito, N. *Chem. Lett.* **1972**, 369–379. (c) Kill, R. J.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 755–757. (d) Kosower, E. M.; Teuerstein, A.; Burrows, H.; Swallow, A. J. *J. Am. Chem. Soc.* **1978**, *100*, 5185. (e) van Eikeren, P.; Kenney, P.; Tokmakian, R. *Ibid.*, in press.

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New Membrane Carrier for Selective Transport of Metal Ions

Sir:

Transport of metal ion across a membrane plays an important role in biology and may have useful practical applications to separation science. The selective and specific transport of alkali metal ions has already been realized by using synthetic or naturally derived cyclic multidentate ligands as membrane carriers.[1] On the other hand, little attention has been directed toward the transport of transition and heavy metal ions[2] which are important from the biochemical and medical points of view. Hence, the development of a new membrane carrier for selective transport of these metal ions is still a challenging problem.

We report here a selective liquid membrane system containing a new linear multidentate carrier for transporting transition and heavy metal ions, and present an example of an in vitro system which exhibits characteristics of biological transport. Previously we have reported the synthesis and metal binding properties of a new class of octameric oligomers having the structure $[CH_2CH_2N(CXNHPh)]_{n=8}$ (X = O or S). These linear octamers were prepared by ring-opening oligomerization[3,4] and could make complexes selectively with copper(II) and mercury(II) ions.[4,5] Such a specific binding property of the new octamers fits with the requirement for a selective carrier. Moreover, the intrinsic flexible nature of linear carrier may permit conformational changes in the binding and releasing processes of metal ions, as suggested by Tümmler et al.[6]

Two octameric carriers, **1** and **2**, and their analogue, **3**, were used as membrane carriers (see Figure 1). The "liquid membrane" system operated here is shown schematically in Figure 2.[7] The carriers, **1**–**3**, are much less soluble in the surrounding solutions (aqueous phases I and II) than in the CH_2Cl_2 "membrane". After complexation of the carrier with metal ion on the left side of the membrane, the complex slowly diffuses down its concentration gradient. On the right side of the membrane, metal ion may be extracted into the aqueous phase II, via formation of a ternary complex (carrier-metal ion-amino acid). Then the free carrier diffuses back across the membrane. The net result is that metal ion is moved from the aqueous phase I (left) to the aqueous phase II (right) across the bulk organic phase (liquid membrane).

The copper(II) ion was transported with surprisingly high

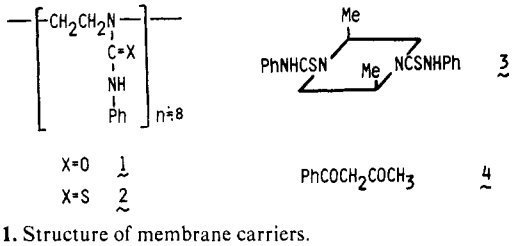

Figure 1. Structure of membrane carriers.

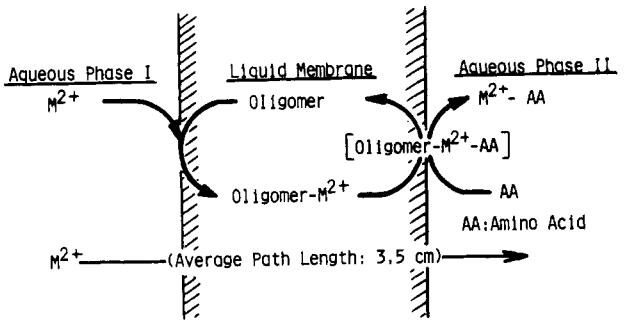

Figure 2. Liquid membrane system.

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