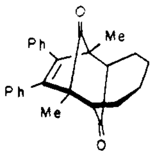
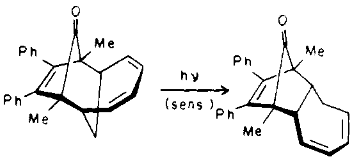
sigmatropic shifts.[10] The photochemical [6 + 4] cycloreversion of **1** is also a photochemically forbidden reaction. Notably, **1**, which undergoes the [6 + 4] cycloreversion upon direct irradiation, thermally dissociates slowly at room temperature, while **3**, which does not photodissociate, is stable above 100°.

Minor modifications of functionality in these systems result in altered photochemical reactivity. In particular, both the diene and stilbene moieties must be present for the [3,3] rearrangement to occur. Thus, the tetrahydro derivative **9**[4] appears quite stable to prolonged irradiation[6c] in the absence of oxygen,[11] in contrast to the more strained 2,3-diphenylnorbornen-7-ones which readily decarbonylate in solution.[12] Moreover, the cyclopentadiene–tropone [6 + 4] adduct displays entirely different photochemical behavior which will be reported at a later date.



9



10 11

Photolysis of the cycloheptatriene [6 + 4] adduct **10**[3,6a,c] results in formation of **11**[3] in about 15% yield in addition to other minor products. However, none of the product expected from dissociation, **6**, is observed in these reactions. This formation of **11** is formally a [1s,5s] sigmatropic carbon shift, a further example of a photochemically forbidden process in these systems.[13] Remarkably, the thermolysis of **10** results in a thermally forbidden [1s,3s] sigmatropic shift, presumably involving a diradical intermediate.[3]

Observation of forbidden reactions is usually considered evidence for diradical or dipolar intermediates. In the present case, the cleavage of the 1,6 bonds in **1**, **3**, and **10** would result in formation of stabilized diradicals. However, the selective collapse of these diradicals to different products when generated from excited states of different multiplicities would constitute spin correlation effects of unexpected proportions.[14] Alternative mechanistic rationales for these reactions involving different diradical intermediates or concerted mechanisms are the subject of continuing studies.

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(10) Photochemical Cope rearrangements have been observed previously: W. Eberbach and H. Prinzbach, *Helv. Chim. Acta*, 50, 2490 (1967); *Chimia*, 22, 502 (1968); H. N. S. Rao, N. P. Damodaran, and S. Dev., *Tetrahedron Lett.*, 227 (1967); H. R. Ward and E. Karafliath, *J. Amer. Chem. Soc.*, 91, 522 (1969); A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *ibid.*, 91, 6858 (1969); O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *ibid.*, 91, 6856 (1969).

(11) In the presence of traces of oxygen or iodine, **9** undergoes conversion to a phenanthrene derivative, a well-documented reaction of *cis*-stilbene singlets: F. R. Stermitz, "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 247.

(12) C. M. Anderson, J. B. Bremner, H. H. Westberg, and R. N. Warrener, *Tetrahedron Lett.*, 1585 (1969); I. W. McCay and R. N. Warrener, *ibid.*, 4779 (1970); B. Fuchs, *Isr. J. Chem.*, 6, 517 (1968), and references therein.

(13) The conversion of **10** to **11** involving a sequence of photochemically allowed [1s, 3s] sigmatropic shifts cannot be discounted at this time.

(14) D. I. Schuster, G. R. Underwood, and T. P. Knudsen, *J. Amer. Chem. Soc.*, **93**, 4304 (1971).

Reactions of Dihydronicotinamides. I. Evidence for an Intermediate in the Reduction of Trifluoroacetophenone by 1-Substituted Dihydronicotinamides

Sir:

Many oxidation–reduction reactions of models for the nicotinamide coenzymes involve direct hydrogen transfer without exchange with solvent protons, and show none of the properties of radical-chain processes.[1] Such reactions, and the related enzymic processes, are therefore usually considered to be "hydride transfers,"[2] although the evidence does not demonstrate that the transfer of the proton and two electrons is concerted. We present here evidence which requires that one particular "hydride transfer," the reduction of trifluoroacetophenone to trifluoromethylphenylcarbinol by some 1-substituted-1,4-dihydronicotinamides[3,4] be a two-step process.

The reaction was studied in 25% (v/v) isopropyl alcohol–water with 0.1*M* triethanolamine–0.1 *M* triethanolamine hydrochloride buffer and an ionic strength of 0.50 *M* at 50.0 ± 0.2°. In the presence of excess trifluoroacetophenone, the disappearance of dihydronicotinamide (spectrophotometric at 355 nm) follows first-order kinetics over three half-lives.[4] The first-order rate for a given dihydronicotinamide is the sum of two terms[4] (eq 1). The first term is due to hydration of the dihydronicotinamide and is the rate observed in the absence of ketone.[5] The second is due to the reduction of the ketone; >95% of the carbinol predicted by kinetics can be detected by glpc analysis at the end of a reaction.[4] The oxidation–reduction involves direct transfer of hydrogen, and is not affected by the addition of free-radical chain inhibitors.[3] Although trifluoroacetophenone is extensively hydrated in aqueous solution,[6] the formation of free ketone is not at all rate determining in our experiments, which show clear first-order dependence on dihydronicotinamide concentration.

$$k_{\text{obsd}} = k_{\text{hyd}} + k_{\text{r}}[\text{trifluoroacetophenone}] \qquad (1)$$

The calculated second-order constants k_{r} for the reduction of trifluoroacetophenone by three dihydronicotinamides and 4-monodeuteriodihydronicotin-

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(1) See, for instance: (a) D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.* 77, 2261 (1955); (b) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *ibid.*, **79**, 712 (1957); (c) B. E. Norcross, P. E. Kleindienst, Jr., and F. H. Westheimer, *ibid.*, **84**, 797 (1962); (d) K. A. Schellenberg and G. W. McLean, *ibid.*, **88**, 1077 (1966); (e) R. W. Huffmann and T. C. Bruice, *ibid.*, **89**, 6243 (1967).

(2) H. Sund in "Biological Oxidations," T. P. Singer, Ed., Wiley-Interscience, New York, N. Y., 1968, pp 621–624.

(3) T. P. Goldstein, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 11–16, 1966, Abstract C196, and personal communications.

(4) J. J. Steffens, Ph.D. Thesis, Massachusetts Institute of Technology, 1971; J. J. Steffens and D. M. Chipman, in preparation.

(5) C. C. Johnston, J. L. Gardner, C. H. Seulter, and D. E. Metzler, *Biochemistry*, 2, 689 (1963).

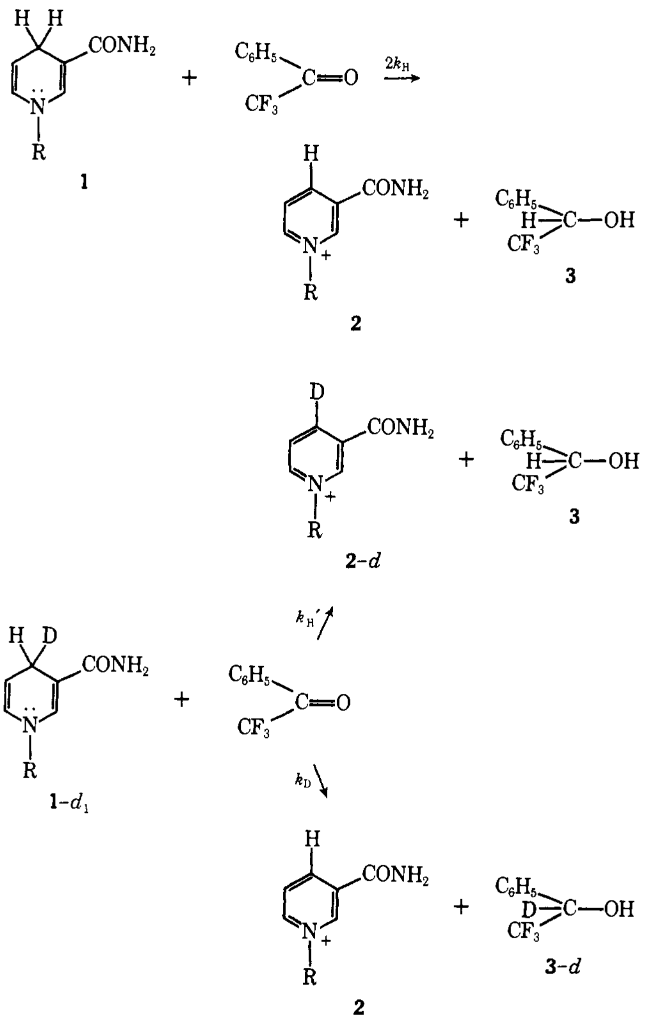
(6) R. Stuart and R. Van der Linden, *Can. J. Chem.*, **38**, 399 (1960).

Table I. Kinetic and Product Analysis Data for Reactions of Dihydronicotinamides with Trifluoroacetophenone[a]

		k_r, M^{-1} min^{-1} [b]				
(Compd)	R	**1**	**1**-d_1	$k_r/k_r^{d_1}$	"k_H/k_D"[c]	(**3**/**3**-d)[d]
1a	n-Pr	0.252 ± 0.007	0.218 ± 0.003	1.16 ± 0.04	1.38 ± 0.11	3.8 ± 0.3
1b	Bz	0.0813 ± 0.0022	0.0552 ± 0.0042	1.47 ± 0.12	2.77 ± 0.85	3.8 ± 0.3
1c	2.6-Di-ClBz	0.0380 ± 0.0007	0.0226 ± 0.0010	1.68 ± 0.08	5.25 ± 0.56	

[a] At 50° in 25% (v/v) isopropyl alcohol, 0.1 M triethanolamine–0.1 M triethanolamine hydrochloride, $\mu = 0.5\ M$. [b] Second-order rate constants from dependence of k_{obsd} on [trifluoroacetophenone]. Experimental details in ref 4. Errors are standard deviations. [c] Calculated from $k_r/k_r^{d_1}$ using eq 3, and assuming $k_H/k_H' = 1$. [d] Isotopic ratio in carbinol from reduction with **1**-d_1, corrected for isotopic content of **1**-d_1 used.

Scheme I



amides are listed in Table I. If the mechanism involves simple hydride transfer (Scheme I), we can write eq 2 and 3. Equation 3 allows us to calculate the primary isotope effect, k_H/k_D, given in the sixth column of Table I, if we assume that the secondary isotope effect, k_H/k_H', is approximately 1. The dramatic change in primary

$$k_r/k_r^{d_1} = 2k_H/(k_H' + k_D) \tag{2}$$

$$k_H/k_D = (k_r/k_r^{d_1})/[2 - (k_r/k_r^{d_1})(k_H'/k_H)] \tag{3}$$

hydrogen isotope effect is unprecedented,[7] and it is difficult to believe that the transition state for a reaction could vary as suggested by these effects with so little change in overall rate.[8]

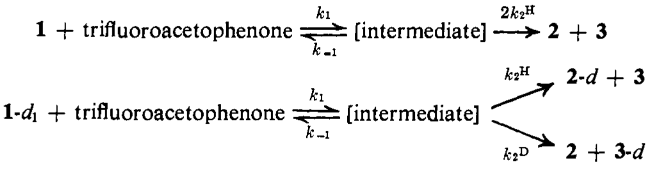
The partitioning of the isotopes into products provides stronger evidence against a one-step reaction. A solution of 2 × 10^{-3} M monodeuteriodihydronicotinamide (**1**-d_1) and 0.10 M trifluoroacetophenone is allowed to react for more than eight half-lives. Under these conditions, about 75% of the dihydronicotinamide reacts with ketone to produce carbinol, with the remainder undergoing hydration.[4] Crude carbinol contaminated with some ketone is separated from salts, etc., by extraction, and analyzed by mass spectroscopy with spectra of authentic compounds as references. Two reaction mixtures for each compound were run, and each mixture was analyzed several times. A small correction (<10%) must be introduced to account for the slight isotopic impurity of our samples of **1**-d_1,[9] and the data in the last column of the table are values of (**3**/**3**-d) corrected to reflect the partitioning of pure **1**-d_1.

The kinetic and isotope partitioning data for propyldihydronicotinamide are not consistant with Scheme I, which predicts that the kinetic and partitioning data be related by eq 4. This equation holds for **1a** only if the

$$k_r/k_r^{d_1} = 2(k_H/k_H')/[1 + (\mathbf{3}\text{-}d/\mathbf{3})] \tag{4}$$

secondary isotope effect, k_H/k_H', is 0.73 ± 0.03. An α secondary isotope effect of this sort can be discounted, particularly for the conversion of an sp^3- to an sp^2-hybridized carbon.[10] The one-step mechanism of Scheme I can thus be rejected.

Scheme II



$$\mathbf{1} + \text{trifluoroacetophenone} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{intermediate}] \xrightarrow{2k_2^H} \mathbf{2} + \mathbf{3}$$

$$\mathbf{1}\text{-}d_1 + \text{trifluoroacetophenone} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{intermediate}] \begin{cases} \xrightarrow{k_2^H} \mathbf{2}\text{-}d + \mathbf{3} \\ \xrightarrow{k_2^D} \mathbf{2} + \mathbf{3}\text{-}d \end{cases}$$

The simplest alternative, involving an intermediate, is Scheme II. The kinetic isotope effect and isotope partitioning predicted by this scheme are given in eq 5 and 6;[11] the relation between the two depends on whether k_1 or k_2 is rate determining. The data pre-

$$k_r/k_r^{d_1} = \frac{2k_2^H}{(k_2^H + k_2^D)} \frac{(k_{-1} + k_2^H + k_2^D)}{(k_{-1} + 2k_2^H)} \tag{5}$$

$$(\mathbf{3}/\mathbf{3}\text{-}d) = k_2^H/k_2^D \tag{6}$$

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(7) See, for instance: E. S. Lewis, J. M. Perry, and R. H. Grinstein, *J. Amer. Chem. Soc.*, **92**, 899 (1970); J. E. Dixon and T. C. Bruice, *ibid.*, **92**, 905 (1970), and references therein.

(8) The assumption $k_H/k_H' = 1$ does not affect the argument; any reasonable value for k_H/k_H' generates a wide variation in calculated k_H/k_D for the series.

(9) Corrections to the *kinetic* constants due to isotopic inhomogeneity of starting materials are negligible.

(10) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960, p 87ff; A. Streitwiesser, R. H. Jagow, R. C. Fahay, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(11) Secondary isotope effects are ignored here for simplicity's sake.

sented above are consistent with this scheme, if k_2 is rate determining for the 2′,6′-dichlorobenzyl compound **1c**, but k_1 has become partly rate determining for the propyl compound **1a**.

It has been suggested that some biochemical oxidation–reduction reactions, particularly those involving flavins,[12] proceed *via* covalent adducts of the reactants. The intermediate of Scheme II cannot be covalent, however. Addition of a group to the pyridine ring in **1**-d_1 must occur either cis or trans to the deuterium atom; the intermediate is then committed either to transfer of the hydrogen *or* the deuterium. A mechanism involving addition of the ketone to the dihydropyridine moiety thus requires two *separate* intermediates, and it can be shown that for such a mechanism, the same relation between kinetic and isotopic partitioning results predicted by Scheme I must hold.

We propose a mechanism involving a common intermediate (or mixture of intermediates) to rationalize the data presented above. We suggest that the intermediate is a noncovalent charge-transfer complex, and that in the first step there is at least some degree of electron transfer from the dihydropyridine to the ketone. The formation of products from the intermediate involves transfer of the hydrogen nucleus and completion of the transfer of electrons, and has a kinetic isotope effect associated with it. The participants in the complex must be capable of some motion relative to one another within a solvent cage, so that either hydrogen may be transferred.[13a] Kosower[13b] has analyzed the energetics of such a one-electron mechanism for reduction of acetaldehyde by a dihydropyridine, and concluded that it is plausible.

Our mechanistic suggestion may be relevant to other dehydrogenase model reactions. Most ordinary ketones are not readily reduced by dihydronicotinamides in the absence of enzymes, and those compounds which are[14] have extensive delocalized π systems with low-lying empty orbitals. It seems likely to us that in all these reactions the electrons are transferred *via* interaction between the conjugated π systems of the reactants, rather than in close coordination with the hydrogen nucleus. The role that an enzyme plays in making possible reactions between reduced nicotinamide coenzymes and *simple* carbonyl compounds remains an intriguing puzzle. Spectroscopic evidence suggests that aromatic residues in certain dehydrogenases are capable of strong electronic interactions with the pyridine moiety of bound coenzyme.[15] One can imagine processes in which electronic interaction between coenzyme, substrate, and enzyme allows the separation of electron transfer and proton transfer in these enzymic reactions as well.

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[12] G. A. Hamilton and L. E. Brown, *J. Amer. Chem. Soc.*, **92**, 7225 (1970).

[13] (a) Ion pairs capable of relative motion without separation have been proposed in other connections; see, for instance, D. J. Cram, "Fundamentals of Carbonion Chemistry," Academic Press, New York, N. Y., 1965, p 98 ff. (b) E. M. Kosower, *Progr. Phys. Org. Chem.*, 3, 81 (1969).

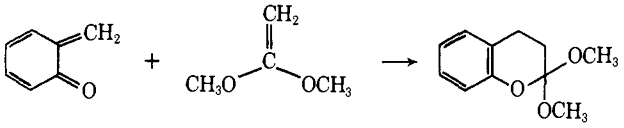
[14] See T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, p 343 ff.

[15] E. Racker and I. Krimsky, *J. Biol. Chem.*, **198**, 731 (1952); C. Cilento and P. Tedeschi, *ibid.*, **236**, 907 (1961); S. Shifrin and N. O. Kaplan, *Advan. Enzymol.*, **22**, 337 (1960); A. U. Bertland 2nd, *Biochemistry*, **9**, 4649 (1970).

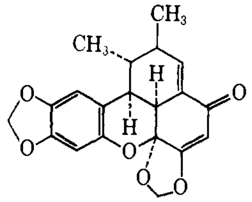
The Total Synthesis of Carpanone

Sir:

We described recently a facile, high-yield reaction of *o*-quinonemethide with nucleophilic olefins such as 1,1-dimethoxyethylene.[1] The total synthesis of carpanone provides an intramolecular example of the utility of this reaction.



Carpanone (**1**), a lignan obtained from the bark of the carpano tree,[2] poses a significant synthetic challenge. The molecule possesses no element of symmetry and has five contiguous asymmetric centers. In analyzing the problem, one can imagine the benzodioxane ring to be formed by nucleophilic attack of an enol ether unit on an *o*-quinonemethide (**2**). This approach has particular appeal because it may be related to the biosynthesis of carpanone.[2] The required precursor **2** has a C_2 axis of symmetry which passes through the midpoint of the bond joining the two *o*-quinonemethide units but has neither a center nor a plane of symmetry. Synthesis of a reactive species such as the bis-*o*-quinonemethide (**2**) is a formidable task, but Barton's brilliant synthesis of usnic acid[3] suggests that phenolic coupling might succeed. Two problems must be faced in this approach. First, coupling must occur on the styryl double bond rather than the aromatic ring, and, second, the coupling process forms two asymmetric centers which must have the correct stereochemistry. Actually, the stereochemical problem is more difficult than it first appears because the stereochemistry at all centers is determined in the formation of the first bond.



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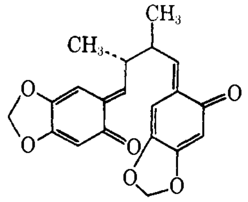

2

The required 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol (**3**, mp 87–88°) was prepared from 2-allyl-

[1] O. L. Chapman and C. L. McIntosh, *Chem. Commun.*, 383 (1971).

[2] G. C. Brophy, J. Mohandas, M. Slaytor, S. Sternhell, T. R. Watson, and L. A. Wilson, *Tetrahedron Lett.*, 5159 (1969).

[3] D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Amer. Chem. Soc.*, **78**, 530 (1956).