by preparation[26,27] of the authentic compound from cyclopentyl methanesulfonate[27,28] and was identified by chemical analysis, ^{1}H NMR, and high-resolution mass spectroscopy: m/z 102.06805 (calcd m/z 102.06808). In the other instances the ^{1}H NMR spectrum of the hydroperoxide obtained by the present reactions (in D_2O) was compared with those of samples as obtained in $CDCl_3$.[11] Alkyl hydroperoxides were also determined by iodometric titration.[29,30]

Kinetics. A Cary 219 spectrophotometer was used to monitor the overall reaction rate by recording the time-dependent absorbance at a wavelength in the range 300–340 nm. Pseudo-first-order rate constants were calculated by a least-squares fit of the data to the standard equation $\ln (D_t - D_\infty) = \ln (D_0 - D_\infty) - k_{obsd}t$. In these studies the temperature was controlled by water circulating through a jacketed cell holder, and lithium perchlorate was added to maintain the ionic strength constant at 1.00 M.

In addition, the rate of production of the ketone was determined using a GC technique for two of the reactions. These runs were performed with an added internal standard on a 10% FFAP column.

Acknowledgment. This work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Chemical Sciences Division (Contract No. W-7405-ENG-82, WPAS-KC-03-02-01). We acknowledge helpful discussions with Professor W. S. Trahanovsky and are grateful to a referee for calling our attention to ref 23.

Supplementary Material Available: Tables giving analytical, NMR, and kinetic data (12 pages). Ordering information is given on any current masthead page.

(26) Medweden, S. S.; Alexejewa, E. N. *Ber. Dtsch. Chem. Ges. B* **1932**, *65*, 133.
(27) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2990, 2984.
(28) Sekera, V. C.; Marvel, C. S. *J. Am. Chem. Soc.* **1933**, *55*, 345.

Reduction by a Model of NAD(P)H. 29. Kinetics and Isotope Effects for the Reduction of Substituted Trifluoroacetophenone

Atsuyoshi Ohno,* Hiroyuki Yamamoto, and Shinzaburo Oka

Contribution from the Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan.
Received March 10, 1980

Abstract: Kinetics for the reduction of substituted and unsubstituted α,α,α-trifluoroacetophenone by a model of NAD(P)H in acetonitrile in the presence and absence of a magnesium ion, a catalyst, has been studied. The catalyzed and uncatalyzed reactions show linear free-energy relationships. It is found that the magnesium ion retards the reaction of certain substituted trifluoroacetophenones. The kinetic isotope effect and the isotopic ratio in the product are also studied. These values vary depending on the substituent and on the presence or absence of the magnesium ion. The result indicates that there is at least one intermediate in the reaction and is discussed in relation to the stability of the intermediate as well as that of the transition states.

The pioneering study by Abeles et al.[1] on the mechanism of biomimetic reduction with a NAD(P)H model compound proposed that the reduction proceeds through one-step hydride transfer. Later Steffens and Chipman found that the kinetic deuterium isotope effect was much smaller than the H/D isotopic ratio in the product and proposed that there is at least one intermediate in the reduction.[2] Based on an ESR study, we claimed that the intermediate suggested by them is a charge-transfer-type complex.[3,4] Recently our claim was questioned on the basis that both the model compound and other tertiary amines behaved similarly in a spin-trapping experiment.[5] However, the model compound, a 1,4-dihydropyridine derivative, is also a tertiary amine.[6]

The rates for one-electron transfer from a photoexcited model compound to a variety of substrates were found to be much slower than those for chemical reductions.[7] However, the existence of a small but appreciable kinetic deuterium isotope effect[2,8,9] proves that the one-electron transfer involved in the chemical reaction differs completely from that in the photophysical process, where the movement of an electron is controlled by the Franck–Condon principle. Thus, it has been almost established that an electron and a hydrogen nucleus (in the form of a hydrogen atom or a proton) move separately in the reduction.

It has been found that bivalent metal ions such as magnesium and zinc catalyze the reduction of certain substrates,[10,13] whereas

Table I. Rate Constants for the Reduction of α,α,α-Trifluoroacetophenone (1a) with PNAH in Acetonitrile at 50 °C[a]

10^2[1a], M	10^2[$Mg(ClO_4)_2$], M	10^3k_{obsd}, min^{-1}	10^3k_{corr}, min^{-1}	10^2k, M^{-1} min^{-1}
0.00	2.00	0.506		
2.02	2.00	1.76	1.25	6.20
4.50	2.00	3.27	2.76	6.14
6.40	1.00	4.50	3.99	6.24
6.40	2.00	4.60	4.09	6.40
6.40	4.04	4.52	4.01	6.27
6.40	6.93	4.52	4.01	6.27
7.82	2.00	5.16	4.65	5.95
9.04	2.00	5.90	5.39	5.97
10.20	2.00	6.89	6.38	6.26
				6.18[c] ± 0.139[b]

[a] [PNAH] = 1.00×10^{-4} M. Standard deviation for each kinetic run was less than 3%. [b] Standard deviation. [c] Mean value.

(1) Abeles, R. H.; Hutton, R. F.; Westheimer, F. H. *J. Am. Chem. Soc.* **1957**, *79*, 712–716.
(2) Steffens, J. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 6694–6696.
(3) Ohno, A.; Kito, N. *Chem. Lett.* **1972**, 369–372.
(4) Ohnishi, Y.; Ohno, A. *Chem. Lett.* **1967**, 697–700.
(5) Hood, R. A.; Prince, R. H.; Rubinson, K. A. *J. Chem. Soc., Chem. Commun.* **1978**, 300–301.
(6) Ohnishi, Y.; Kagami, M.; Numakunai, T.; Ohno, A. *Chem. Lett.* **1976**, 915–916.
(7) Martens, F. M.; Verhoeven, J. W.; Gase, R. A.; Pandit, U. K.; de Boer, Th. *Tetrahedron* **1978**, *34*, 443–446.
(8) Creighton, D. J.; Hajdu, J.; Sigman, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 4619–4625.
(9) Okamoto, T.; Ohno, A.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1977**, 181–182.
(10) Ohnishi, Y.; Kagami, M.; Ohno, A. *J. Am. Chem. Soc.* **1975**, *97*, 4766–4768.

0002-7863/81/1503-2041$01.25/0

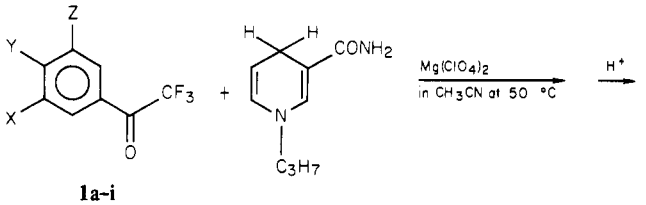
these metal ions retard the reduction of others.[14,16] There are substrates that belong to a third category. With these substrates the rate of reduction is affected by the metal ion in such a way that the rate increases, comes to a maximum, and then decreases as the concentration of the metal ion is increased.[17-19]

The results mentioned above have been interpreted in terms of the stability of the substrate–metal ion model ternary complex.[20,21] It has also been proposed that the metal ion accelerates the transfer of an electron from the model to the substrate.[20,22,23] The argument, however, is based on the results from dissimilar reaction conditions, with solvents, substrates, and models of different types. Consequently, the discussion was not free from ambiguities.

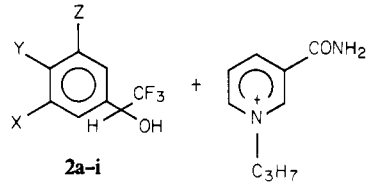
In order to obtain further insight into the mechanism of the reduction, we studied the reduction of substituted and unsubstituted α,α,α-trifluoroacetophenone with 1-propyl-1,4-dihydronicotinamide (PNAH) in acetonitrile. The results have revealed various characteristics of the reduction of a variety of substitutents on α,α,α-trifluoroacetophenone. That is, the acceleration and deceleration of reaction rate caused by the metal ion, the coincidence and discrepancy between the kinetic isotope effect and the isotopic distribution in the product, and the dependency of the kinetic isotope effect in the presence or absence of the metal ion can be explained by a uniform mechanism.

Results

Pseudo-first-order rate constants, k_{obsd}, under various concentrations of **1a** and magnesium perchlorate are listed in Table I.



1a–i PNAH



2a–i PNA^+

a, X = Y = Z = H; b, X = Z = H, Y = Cl; c, X = Z = H, Y = Br; d, X = F, Y = Z = H; e, X = Br, Y = Z = H; f, X = CF_3, Y = Z = H; g, X = NO_2, Y = Z = H; h, X = CF_3, Y = H, Z = NO_2; i, X = Z = NO_2, Y = H

The observed rate constants were corrected for the rate constant for the magnesium ion catalyzed decomposition of PNAH (5.06×10^{-4} min^{-1}). The values, k_{corr}, are also listed in Table I together with second-order rate constants, k, calculated by dividing k_{corr} by the concentration of **1a**. It is obvious that the rate is first order in PNAH, first order in **1a**, and zero order in magnesium perchlorate in the range of concentrations employed.[13] Other substrates behaved similarly. The second-order rate constants are summarized in Table II.

Kinetics was also studied with PNAH-*4-d* and PNAH-*4,4-d*$_2$. For runs with PNAH-*4-d* at least three different concentrations

Table II. Second-Order Rate Constants for Substituted and Unsubstituted α,α,α-Trifluoroacetophenone in Acetonitrile at 50 °C with and without the Magnesium Ion[a]

substrate	$10k$, M^{-1} min^{-1} without Mg^{2+}	$10k$, M^{-1} min^{-1} with Mg^{2+} [b]
1a	[c]	0.618 ± 0.0139
1b	0.153 ± 0.0083	1.11 ± 0.018
1c	0.158 ± 0.0059	1.53 ± 0.041
1d	0.255 ± 0.0036	1.95 ± 0.073
1e	0.470 ± 0.0005	2.59 ± 0.033
1f	0.741 ± 0.0139	2.84 ± 0.035
1g	2.98 ± 0.062	6.43 ± 0.127
1h	28.2 ± 1.77	16.4 ± 0.456
1i	(80.3 ± 3.00)[d]	52.8 ± 2.66

[a] Errors are standard deviations. [b] 2.0×10^{-2} M. [c] The reaction was too slow to be followed kinetically. The calculated value is 2.70×10^{-3} M^{-1} min^{-1} (cf. Figure 1). [d] Rate constant for net reaction. See text for detail.

Table III. Second-Order Rate Constants for PNAH-*4-d* and PNAH-*4,4-d*$_2$ in Acetonitrile at 50 °C with and without the Magnesium Ion[a]

substrate	x in PNAH-d_x[b]	$10k$, M^{-1} min^{-1} without Mg^{2+}	$10k$, M^{-1} min^{-1} with Mg^{2+} [c]
1a	1		0.393 ± 0.0010
	2		0.213 ± 0.0005
1b	1	0.110 ± 0.0039	0.727 ± 0.0125
	2	0.0752 ± 0.0027	
1c	1	0.111 ± 0.0055	1.05 ± 0.030
1d	1	0.173 ± 0.0047	1.31 ± 0.057
1e	1	0.313 ± 0.0017	1.75 ± 0.009
	2	0.210 ± 0.0013	1.12 ± 0.006
1f	1	0.486 ± 0.021	1.83 ± 0.026
1g	1	1.96 ± 0.065	4.21 ± 0.060
1h	1	18.9 ± 1.22	11.0 ± 0.50
1i	1	(49.8 ± 1.58)[d]	35.1 ± 2.26

[a] Errors are standard deviations. [b] The isotopic purity of PNAH-*4,4-d*$_2$ was 90.0%. [c] 2.0×10^{-2} M. [d] Rate constant for net reaction. See text for detail.

Table IV. Isotope Effects, k^H/k^D and Y^H/Y^D, for the Reduction of Substituted and Unsubstituted α,α,α-Trifluoroacetophenone in Acetonitrile at 50 °C with and without the Magnesium Ion[a]

substrate	without Mg^{2+} k^H/k^D	without Mg^{2+} Y^H/Y^D	with Mg^{2+} k^H/k^D	with Mg^{2+} Y^H/Y^D
1a	[b]	3.7	3.68	3.4
1b	2.29	3.6	3.23	3.1
1c	2.47	3.0	2.68	3.5
1d	2.78	3.7	2.87	3.4
1e	2.99	3.0	2.85	3.0
1f	3.20	3.4	3.46	3.5
1g	3.17	3.4	3.23	3.2
1h	2.98	3.4	2.91	3.0
1i	(4.12)[c]		3.04	3.9
		3.4[e] ± 0.3[d]	3.11[e] ± 0.30[d]	3.4[e] ± 0.3[d]

[a] Estimated errors are ±4% for k^H/k^D and ±7% for Y^H/Y^D. Secondary kinetic isotope effect is calculated to be 1.03 ± 0.05. [b] k^H/k^D = 1.38 and Y^H/Y^D = 3.8 in 25% aqueous 2-propanol.[2] [c] Isotope effect for net reaction. See text for detail. [d] Standard deviation. [e] Mean values.

(11) Ohnishi, Y.; Kagami, M.; Ohno, A. *Tetrahedron Lett.* **1975**, 2437–2440.
(12) Ohnishi, Y.; Numakunai, T.; Ohno, A. *Tetrahedron* **1975**, 3813–3814.
(13) Ohno, A.; Yamamoto, H.; Okamoto, T.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2385–2386.
(14) Dittmer, D. C.; Lombardo, A.; Batzold, F. H.; Greene, C. S. *J. Org. Chem.* **1976**, *41*, 2976–2981.
(15) Ohno, A.; Yasui, S.; Nakamura, K.; Oka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 290–293.
(16) Shinkai, S.; Ide, T.; Hamada, H.; Manabe, O.; Kunitake, T. *J. Chem. Soc., Chem. Commun.* **1977**, 848–849.
(17) Gase, R. A.; Boxhoorn, G.; Pandit, U. K. *Tetrahedron Lett.* **1976**, *2889*–2892.
(18) Huges, M.; Prince, R. H. *J. Inorg. Nucl. Chem.* **1978**, *40*, 703–712.
(19) Ohno, A.; Yasui, S.; Gase, R. A.; Oka, S.; Pandit, U. K. *Bioorg. Chem.* **1980**, *9*, 199–211.
(20) Ohno, A.; Kimura, T.; Yamamoto, H. Kim, S. G.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1535–1538.
(21) Ohno, A.; Yasui, S.; Yamamoto, H.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 294–296.
(22) Okamoto, T.; Ohno, A.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1977**, 784–786.
(23) Ohno, A.; Yamamoto, H.; Okamoto, T.; Oka, S.; Ohnisihi, Y. *Chem. Lett.* **1978**, 65–68.

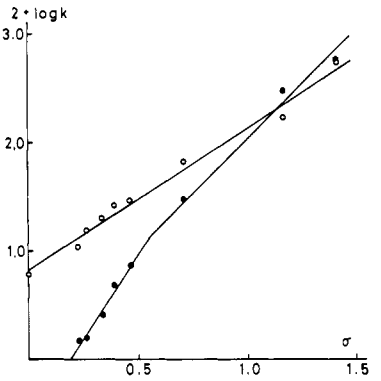


Figure 1. Hammett plot for the reduction of substituted and unsubstituted α,α,α-trifluoroacetophenone in the presence (○) and absence (●) of magnesium perchlorate.

of substrates were employed, and the kinetic isotope effects, k^H/k^D, were calculated by using Steffens and Chipman's equation.[2] The second-order rate constants for deuterated PNAH's are summarized in Table III. Table IV lists the calculated kinetic isotope effects as well as isotopic ratios in the products, Y^H/Y^D. The kinetic isotope effect was not corrected for the secondary deuterium isotope effect.[24] The deuterium content on the benzylic carbon of the product, **2**, was observed by mass spectrometry.

The reduction of *m,m'*-dinitro-α,α,α-trifluoroacetophenone (**1i**) should be mentioned separately. In the presence of magnesium perchlorate, the reduction took place exclusively at the carbonyl carbon. On the other hand, in the absence of magnesium perchlorate, the reduction of the aromatic ring also took place to some extent.[25] Therefore, it is necessary for **1i** to estimate the rate constant for the reduction of the carbonyl carbon from the observed rate constants and other evidence. The observed k^H/k^D's in the presence and absence of magnesium perchlorate were 3.04 and 4.12, respectively. The value of 3.04 is the real k^H/k^D for the reduction of the carbonyl carbon, because the carbonly carbon is the sole reduction site in the presence of the magnesium ion.[26] Assuming values of 6.45–7.02 for the kinetic isotope effect for the reduction of the aromatic ring, $k_{red}{}^H/k_{red}{}^D$,[27] we obtained the fraction for the reduction of the carbonyl carbon, α, to be 0.68–0.72 according to 1. That is, about 70% of the reduction

$$(kH/k^D)_{obsd} = \alpha(k^H/k^D)_{calcd} + (1 - \alpha)(k_{red}{}^H/k_{red}{}^D) \quad (1)$$

took place on the carbonyl carbon and remaining 30% of the

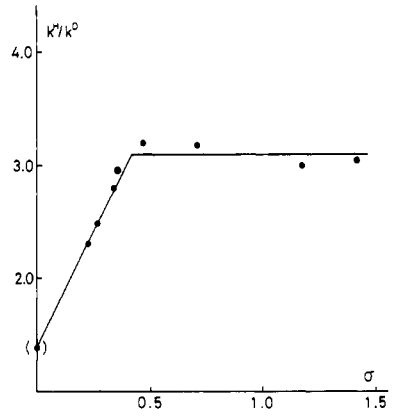


Figure 2. Plots of kinetic isotope effects against substituent constants (σ) for the reduction of substituted and unsubstituted[2] α,α,α-trifluoroacetophenone in the absence of magnesium perchlorate.

reduction proceeded on the aromatic ring. These values were further confirmed by the fact that the yields of the corresponding alcohol and recovered **1i** were 70% and 28%, respectively.

Consequently, we obtained 8.03 M^{-1} min^{-1} × 0.7 = 5.62 M^{-1} min^{-1} for the second-order rate constant for the reduction of **1i** to **2i** with PNAH in the absence of magnesium perchlorate.

Discussion

As shown in Figure 1, plots of rate constants for catalyzed reductions against σ vaues of the substituents give a good straight line with ρ = 1.29 (correlation coefficient r = 0.993). The Hammett plot for uncatalyzed reductions, on the other hand, is composed of two straight lines with ρ_1 = 3.07 (r = 0.985) for substrates with relatively less electron-withdrawing substitutents and ρ_2 = 2.00 (r = 0.995) for those with strong electron-withdrawing substituent(s), respectively. Thus, it is obvious that the uncatalyzed reduction involves more than two processes and the rate-determining step changes from one to another at the boundary of substrates **1d–1f**. Since the ρ_2 value for uncatalyzed reduction is larger than that for catalyzed reduction, two straight lines intersect each other at the point of σ = 1.17, and thereafter the rate constant for uncatalyzed reduction appears to be larger than that for catalyzed reduction. That is, the reduction of α,α,α-trifluoroacetophenone substituted by strongly electron-withdrawing substituent(s) is retarded by the presence of the magnesium ion as was observed for thiopivalophenone, hexachloroacetone, and the *N*-methylacridinium ion.[14-16] Although it is quite reasonable that the uncatalyzed reduction is more sensitive to the substituent effect than the catalyzed reduction,[28] the reversal of rates for catalyzed and uncatalyzed reductions cannot be explained by a one-step mechanism.

The composite property of the reduction can also be recognized by the inspection of isotope effects.[29] The kinetic isotope effects for catalyzed reductions coincide, within experimental error, with the isotopic ratios in the products. This fact means that the process for the transfer of the hydrogen nucleus in the catalyzed reduction constitutes a real transition state. The same is true for the uncatalyzed reductions of (at least) **1f–1i**. On the other hand, the value of k^H/k^D differs from that of Y^H/Y^D in the uncatalyzed reduction of **1b**, which indicates that the transfer of hydrogen nucleus in this reduction is involved in the transition state only partly. The values of k_H/k_D for uncatalyzed reductions are plotted against subsitutent σ values in Figure 2. Here again, as shown in Figure 1, the plots are correlated by two straight lines with **1f** as the break point.

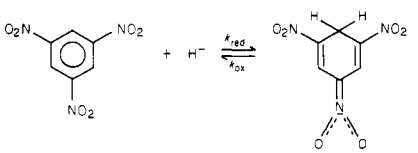
It is noteworthy that the kinetic isotope effect for uncatalyzed reduction of **1a** observed in 25% aqueous 2-propanol[2] locates on

(24) The isotopic ratio in the product, Y^H/Y^D, is a composite of primary and secondary kinetic isotope effects. Therefore, the correction of the kinetic isotope effect, k^H/k^D, by the secondary isotope effect is not necessary for comparison of these two isotope effects. When k^H/k^D is corrected for the secondary isotope effect, the difference between Y^H/Y^D and k^H/k^D becomes larger than those reported herein, in favor of our proposal.

(25) Ohno, A.; Yamamoto, H.; Oka, S. *Tetrahedron Lett.* **1979**, 4061–4064.

(26) Note that k^H/k^D's in the presence and absence of magnesium perchlorate coincide with each other for substrates with a strongly electron-withdrawing substituent.

(27) The kinetic isotope effects for the reduction of 1,3,5-trinitrobenzene, $k_{red}{}^H/k_{red}{}^D$, and reoxidation of the reduction product to 1,3,5-trinitrobenzene, $k_{ox}{}^H/k_{ox}{}^D$, are 7.02 and 10.0, respectively.[25]



It may be safe to expect that the kinetic isotope effects for **1i** and 1,3,5-trinitrobenzene are not much different. Therefore, we estimated 7.02 for $k_{red}{}^H/k_{red}{}^D$ of **1i** as one limit. The other limit was calculated by an equation

$$\frac{k_{red}{}^H}{k_{red}{}^D} = \frac{(Y^H/Y^D)(k_{ox}{}^H/k_{ox}{}^D) - 1}{(k_{ox}{}^H/k_{ox}{}^D) + 1}$$

with an observed value of Y^H/Y^D = 7.2 and estimated value of $k_{ox}{}^H/k_{ox}{}^D$ = 10.0.

(28) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35–154.

(29) Note that the reactions were run in anhydrous acetonitrile and, therefore, were free from side products. Cf. (a) Van Eikeren, P.; Grier, D. L.; Eliason, J. *J. Am. Chem. Soc.* **1979**, *101*, 7406–7409. (b) Chipman, D. M.; Yaniv, R.; Van Eikeren, P. *Ibid.* **1980**, *102*, 3244–3246.

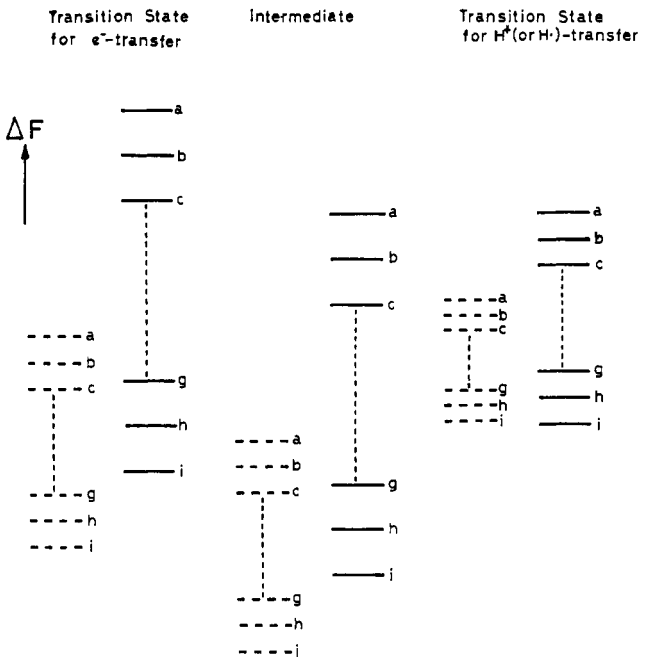


Figure 3. Schematic representation of energy levels for the transition states and intermediate in the presence (---) and absence (—) of magnesium perchlorate.

the straight line formed by those of **1b–1f**, which are observed in acetonitrile. Together with the fact that the values of Y^H/Y^D in 25% aqueous 2-propanol and in acetonitrile are the same, the present result suggests that the position of the hydrogen nucleus at the transition state remains unchanged with a drastic change in solvent character.[30]

The free-energy relationship presently observed for the rate constants and the variation in kinetic isotope effects can be best interpreted by the aid of an energy diagram schematically illustrated in Figure 3.

The reduction is composed of at least two processes: one is an electron transfer (associated with a positive ρ) and the other a hydrogen transfer.[31] In uncatalyzed reductions, at least **1a** and **1b** have higher energy levels for the transition state in the initial step than those in the second step. Since it is the second step that is responsible for the discrimination of isotopes, the diagram explains the smaller k^H/k^D values than the corresponding Y^H/Y^D values for **1a** and **1b**. Whereas substrates **1g–1i** have lower energy levels for the transition state in the initial step than those in the second step, k_H/k_D's for these substrates coincide with corresponding Y^H/Y^D's and remain constant (within undetectable variation). For the substrates **1c–1f**, both transition states have comparable importance for the rate-determining step, and the variation of k^H/k^D only reflects the relative importance of the second step. For an explanation of the predominancy of the initial transition state for one substrate and the second transition state for another one, the energy diagram necessarily predicts that the energy level for the transition state in the initial step is much more sensitive to the substituent effect than that for the second step, which is a reasonable conclusion when one realizes that the second step is the reaction of charged species. Since it is expected that the substituent effect is larger in the intermediate species than in the initial transition state, the diagram predicts another important conclusion: the transition energy for the second step changes with the substituent in such a way that $\Delta F^{\ddagger}_{1a} < \Delta F^{\ddagger}_{1b} < \ldots < \Delta F^{\ddagger}_{1h} < \Delta F^{\ddagger}_{1i}$. That is, on the basis of the diagram, the second step is associated with a negative ρ or the proton transfer is much preferred for this step to hydrogen atom transfer.

In catalyzed reductions, on the other hand, all substrates might have lower transition energies in the initial step than in the second step, because all k^H/k^D's are equal to Y^H/Y^D's, respectively. In other words, the magnesium ion plays a role in catalyzing the initial electron-transfer step with very little effect, if any, on the second, hydrogen-transfer step.[22] Special mention should be made of the catalyzed reductions of **1h** and **1i**. As is expected, these substrates are good electron acceptors.[32] That is, the charge-transfer-type intermediate, $(PNAH)^+ \cdot 1h^- \cdot$ or $(PNAH)^+ \cdot 1i^- \cdot$, is a stable species.[33] The addition of the magnesium ion to this system not only decreases the transition energy for the electron-transfer step (catalysis) but also increases the stability of the intermediate. If the free energy of the intermediate becomes smaller than that of the reactant system in the presence of the magnesium ion, the activation energy in the presence of the magnesium ion becomes larger than that in its absence (inhibition). The magnesium ion not only lowers the energy level of the intermediate but also may increase the level of the transition state in the second step, because positive charges on the magnesium ion may reduce the susceptibility of the reaction center to the effect of substituent(s) (cf. Figure 3). The magnesium ion, therefore, retards the reduction, although the role of the magnesium ion for **1h** and **1i** is the same as that for other substrates.

The present kinetic studies have revealed that the reduction proceeds through a multistep mechanism. The magnesium ion catalyzes the initial electron-transfer process throughout the substrates studied. However, the substituent effect changes the effect of the magnesium ion from net acceleration to net deceleration. We believe that the present result provides a uniform interpretation for results widely reported in the literature.

It may also be suggested that the unreactivity of simple ketones toward the reduction with an NAD(P) H model is mainly due to low potentials of these ketones toward the acceptance of an electron. If there is a device to activate a ketone for one-electron reduction, the succeeding hydrogen transfer may take place spontaneously.

Experimental Section

Melting and boiling points were not corrected. UV, IR, NMR, and mass spectra were recorded on a Union Giken SM-401, Hitachi EPI-S2, JEOL JNM-FX 100, and Hitachi RMU-6E spectrometers, respectively. A Yanaco G-1800F and Varian Aerograph Model 920 were used for VPC.

Materials. Acetonitrile was distilled three times over phosphorus pentoxide and stored over 4A molecular sieves under an atmosphere of argon. Anhydrous magnesium perchlorate was dried at 100 °C and stored in a vacuum desiccator over phosphorous pentoxide. α,α,α-Trifluoroacetophenone (bp 150 °C (760 mm)) (**1a**),[34] *p*-chloro-α,α,α-trifluoroacetophenone (bp 81 °C (20 mm)) (**1b**),[34,35] *p*-bromo-α,α,α-trifluoroacetophenone (bp 95 °C (4 mm)) (**1c**),[35] *m*-bromo-α,α,α-trifluoroacetophenone (bp 78 °C (15 mm)) (**1e**),[36] and *m*-nitro-α,α,α-trifluoroacetophenone (mp 54–55 °C) (**1g**)[36] were prepared according to literature procedures.

m-Fluoro-α,α,α-trifluoroacetophenone (**1d**) and *m*-trifluoromethyl-α,α,α-trifluoroacetophenone (**1f**)[37] were prepared by Grignard reaction from the corresponding aryl bromide and trifluoroacetic acid.[36]

1d: bp 150 °C (760 mm); IR (KBr) 1720 cm^{-1} ($\nu_{C=O}$); NMR in $CDCl_3$ $\delta(Me_4Si)$ 7.60 (m, 4 H).

Anal. Calcd for $C_8F_4H_4O$: C, 50.02; F, 39.56; H, 2.10. Found: C, 49.72; F, 39.83; H, 2.26.

1f: bp 77 °C (50 mm); IR (KBr) 1726 cm^{-1} ($\nu_{C=O}$); NMR in $CDCl_3$ $\delta(Me_4Si)$ 7.92 (m, 4 H).

Anal.[37] Calcd for $C_9F_6H_4O$: C, 44.65; F, 47.08; H, 1.67. Found: C, 43.56, F, 45.39; H, 1.66.

***m*-Nitro-*m'*-trifluoromethyl-α,α,α-trifluoroacetophenone (1h).** Into a flask containing 21.6 g of **1f** was added 40 mL of concentrated sulfuric acid dropwise with stirring. The flask was cooled below 0 °C. Then a mixture of 20 mL of concentrated sulfuric acid, 20 mL of fuming nitric

(30) Van Eikeren, P.; Glier, D. L. *J. Am. Chem. Soc.* **1976**, *98*, 4655–4657.
(31) Since there is no indication for the formation of molecular complexes such as **1a**·PNAH, **1a**·Mg^{2+}, and **1a**·Mg^{2+}·PNAH, the intermediate must be of charge-transfer type as was discussed previously.[3,5] The term "hydrogen" means a hydrogen nucleus. It may be a hydrogen atom or a proton.
(32) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734–745.
(33) Hajdu, J.; Sigman, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 6060–6061.
(34) Park, J. D.; Brown, H. A.; Lacher, J. R. *J. Am. Chem. Soc.* **1951**, *73*, 709–711.
(35) Klabunde, K. J.; Burton, D. J. *J. Org. Chem.* **1970**, *35*, 1711–1712.
(36) Stewart, R.; Van der Linder, R. *Can. J. Chem.* **1960**, *38*, 399–406.
(37) This compound could not be analyzed accurately because of high content of fluorine and of volatility.

acid, and 30 mL of concentrated nitric acid was added dropwise. After the whole mixture was kept at 120 °C for 2 days, the reaction mixture was poured onto 300 g of crushed ice and organic materials were extracted several times with ether. The combined extract was dried over sodium sulfate, and the ether was removed under reduced pressure. The residual liquid was added to a mixture of 5 mL of water and 10 mL of chloroform, and the whole mixture was stirred for 1 h at room temperature. The precipitate was collected and washed several times with chloroform giving 6 g of the hydrate of **1h** (mp 77 °C) as a white solid. The solid was dissolved in 100 mL of toluene, and an azeotropic mixture of toluene and water was removed by distillation. The residue was distilled under reduced pressure giving 4.6 g (20% yield) of **1h** as a yellow liquid: bp 90 °C (8 mm); IR (liquid) 1730 cm^{-1} ($\nu_{C=O}$). NMR in $CDCl_3$ $\delta(Me_4Si)$ 9.70 (s, 1 H), 8.87 (s, 1 H), and 8.63 (s, 1 H).

Anal. Calcd for $C_9F_6H_3NO_3$: C, 37.70; F, 39.70; H, 1.05. Found: C, 37.95; F, 39.44; H, 1.20.

m,m'-Dinitro-α,α,α-trifluoroacetophenone (1i). An attempt to prepare this compound by the nitration of **1g** was unsuccessful. However, the nitration of 1-(*m*-nitrophenyl)-2,2,2-trifluoroethyl alcohol (**2g**) by essentially the same method as described above gave the hydrate of **1i** (mp 70 °C). Azeotropic removal of water from the hydrate gave **1i** in 20% yield as pale yellow crystals; mp 64 °C; IR (KBr) 1740 cm^{-1} ($\nu_{C=O}$); NMR in $CDCl_3$ $\delta(Me_4Si)$ 9.32 (s, 1 H) and 9.14 (s, 2 H).

Anal. Calcd for $C_8F_3N_2O_5$: C, 36.38; F, 21.58; H, 1.14. Found: C, 36.34; F, 21.88; H, 1.17.

1-Aryl-2,2,2-trifluoroethyl alcohols (2a–i). 1-Phenyl-2,2,2-trifluoroethyl alcohol (**2a**) was prepared by the reduction of **1a** with lithium aluminum hydride in 75% yield; bp 95 °C (22 mm).[36] Other alcohols, **2b–i**, were obtained by reducing the corresponding ketones with aluminum 2-propoxide in 2-propanol in 80–90% yields.

1-Propyl-1,4-dihydronicotinamide (PNAH). Syntheses of PNAH, PNAH-*4-d*, and PNAH-*4,4-d_2* have been described in a previous paper.[15] Mass and NMR spectral analyses revealed that the deuterium contents in PNAH-*4-d* and PNAH-*4,4-d_2* were 99.5 ± 0.5 and 90.0 ± 0.5% of the theoretical values, respectively.

Product Analyses. A mixture of a substrate (0.2 mmol) and PNAH (0.2 mmol) in 10 mL of acetonitrile was stirred under an atmosphere of argon in the dark at 50 °C for 1 week in the presence (0.2 mmol) or absence of magnesium perchlorate. Water was added to the mixture, and the solvent was evaporated under reduced pressure. The residue was poured into water and organic materials were extracted with ether. The ether layer was dried over sodium sulfate, and the ether was removed under reduced pressure. Amounts of the substrate remained unreacted and the alcohols produced were quantitatively measured on VPC (Silicon DC-200, 1 m). No other products except for PNA^+ were detected on VPC, TLC (hexane–ethyl acetate 3/1), and NMR. Spectral data of the product alcohols agreed with those of the corresponding authentic samples.

Isotopic Ratio in the Product. Deuterium content in a product alcohol obtained by the reduction with PNAH-*4-d* was analyzed by mass spectrometry on a Simazu LKB-9000 GC-MS spectrometer (SE-52, 1 m). The spectrometer was equipped with a PACK 3000G-b Computing System to calculate the areas of appropriate peaks. At least two different samples were subjected to the spectroscopy, and scans were repeated at least eight times for a sample.

Kinetic Procedure. Acetonitrile was flushed with dry argon prior to use. Solutions for kinetic studies were prepared under an atmosphere of argon and placed in a UV cell (1 cm) equipped with a silicon rubber stopper. The cell compartment of the spectrometer was also filled with dry argon and kept at 50 ± 0.05 °C. As a standard procedure, both sample and reference cells were filled with solutions of a substrate (and magnesium perchlorate, when necessary) in acetonitrile to obtain a difference spectrum. Then, an acetonitrile solution of PNAH was injected into the sample cell by using a syringe to start the reaction. Otherwise the kinetics could not be followed, because the absorption of a substrate was large enough to interfere the observation on the change in the intensity of an absorption (λ_{max} = 354 nm) from PNAH. It was confirmed that the order of incubation of the reagents did not affect the kinetics. The kinetics was followed by observing the decrease in the intensity at 354 nm. However, in runs with high concentrations of a substrate ([S] > 1×10^{-2} M), longer wavelengths were employed for the monitoring (375 nm for **1a–1f**; 384 nm for **1g** and **1h**).

Nevertheless, the change in the intensity of the kinetic solution of **1i** was too small to be followed accurately. Fortunately, the solution showed new absorption with maxima at 440, 464, and 570 nm. The increase in the intensities of new absorptions corresponded to the decrease in the intensity at 354 nm with an isosbestic point at 388 nm.[25] The kinetics for **1i**, therefore, was followed by observing the increase in the intensities at 440 and 464 nm.

All runs gave good first-order plots over 3 half-lives with correlation coefficient better than 0.9995.

Acknowledgment. A.O. thanks the Ministry of Education, Japan, for support of this work.

Supplementary Material Available: Table V, a listing of boiling or melting points and NMR spectral data of the alcohols (1 page). Ordering information is given on any current masthead page.

Reduction by a Model of NAD(P)H. 30. Proof for the Electron–Proton–Electron-Transfer Mechanism

Atsuyoshi Ohno,* Tohru Shio, Hiroyuki Yamamoto, and Shinzaburo Oka

Contribution from the Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan.
Received March 10, 1980

Abstract: Kinetics for the reduction of the *N*-methylacridinium ion by 1-aryl-1,4-dihydronicotinamides in acetonitrile have been studied. The second-order rate constants are linearly correlated with the σ values of substituents. A Hammett-type plot for the kinetic isotope effect affords a Λ-shape correlation with the para methyl substituent as a maximum (k^H/k^D = 5.72), whereas the isotopic partitioning ratio in the product remains constant. The results have been interpreted in terms of an electron–proton–electron-transfer mechanism.

After extensive discussion of the mechanism of reduction with 1,4-dihydropyridine derivatives, it has been proposed that the reduction, in some cases, is most likely composed of initial electron transfer followed by transfer of a hydrogen nucleus.[1-11] In contrast to the initial transfer of an electron, the mechanism of the subsequent process has not yet been well understood. For the re-

(1) Abeles, R. H.; Hutton, R. F.; Westheimer, F. H. *J. Am. Chem. Soc.* **1957**, *79*, 712–716.
(2) Hood, R. A.; Prince, R. H.; Rubinson, K. A. *J. Chem. Soc., Chem. Commun.* **1978**, 300–301.
(3) Martens, F. M.; Verhooven, J. W.; Gase, R. A.; Pandit, U. K.; De Boer, Th. J. *Tetrahedron* **1978**, *34*, 443–446.
(4) Kurz, L. C.; Frieden, C. *Biochemistry* **1977**, *16*, 5207–5216.
(5) Ohno, A.; Kito, N. *Chem. Lett.* **1972**, 369–372.
(6) (a) Creighton, D. J.; Hajdu, J.; Sigman, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 4619–4625. (b) Hajdu, J.; Sigman, D. S. *Ibid.* **1976**, *98*, 6060–6061.
(7) Okamoto, T.; Ohno, A.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1977**, 181–182.
(8) Steffens, J. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 6694–6696.

0002-7863/81/1503-2045$01.25/0