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ISOTOPE EFFECT IN THE REDUCTION OF TRIFLUOROACETOPHENONE[#]

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Kinetic (k_H/k_D) and product (Y_H/Y_D) isotope effects have been studied for the reduction of α,α,α-trifluoroacetophenone with 1-propyl-1,4-dihydronicotinamide in acetonitrile in the presence or absence of magnesium perchlorate. It is concluded that the magnesium ion catalyzes the initial electron-transfer process of the reduction.

In a series of papers[1,2] we proposed a mechanism for magnesium ion-catalysis in the reduction of certain carbonyl compounds with a model of NAD(P)H. The important conclusion proposed in these papers can be summarized as follows:

1. Magnesium ion forms a complex with the model compound activating the latter to release an electron.
2. The reaction is composed of three steps, electron-proton-electron transfers.
3. Magnesium ion catalyzes the initial electron-transfer process.

The third conclusion stems from the facts that the reduction of methyl benzoylformate with a dihydropyridine derivative is accelerated by the presence of magnesium ion[3,4] and that the kinetic deuterium isotope effect, k_H/k_D, for this magnesium ion-catalyzed reduction is as large as the ratio of the yields of protiated to deuterated products, Y_H/Y_D. On the other hand, the reductions of thiopivalophenone[5] and of hexachloroacetone[6] are retarded by the presence of magnesium ion and the values of k_H/k_D for these reductions are as large as those of Y_H/Y_D regardless of the presence or absence of magnesium ion.

Before the above observation is connected to the third conclusion, we need one assumption that uncatalyzed reduction of methyl benzoylformate with a model

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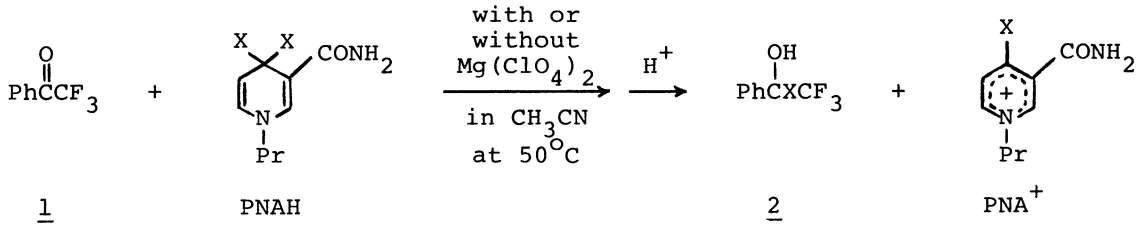
[#] REDUCTION BY A MODEL OF NAD(P)H. Part XVIII.

compound might have smaller value for k_H/k_D than for Y_H/Y_D.[7,8] Unfortunately, however, the reduction of methyl benzoylformate is too slow to be followed kinetically and the assumption has remained with ambiguity.

α,α,α-Trifluoroacetophenone(1) behaves similarly to methyl benzoylformate[9,10] in the bio-mimetic reduction and is a suitable substrate to obtain certification for the assumption. We describe the result from the reduction of 1 with 1-propyl-1,4-dihydronicotinamide(PNAH).



1 PNAH 2 PNA^+

X = H or D

Kinetics was followed spectrophotometrically in acetonitrile at 50±0.05°C by observing the decrease in the intensity at 354 nm with a Union Giken SM-401 Spectrophotometer.[4] As listed in Table 1, it was confirmed that the reaction is first-order in 1, first-order in PNAH, and zero-order in magnesium ion in the range of concentrations employed.[4] Isotopic ratio in the product(2) was obtained by mass spectrometry on a Shimadzu LKB-9000S GC-MS Spectrometer.[5,8,11] The spectrometer was equipped by a PACK 300DG-b Computing System and areas of appropriate peaks were measured. Scans were repeated at least eight times for a sample.[12] The values for k_H/k_D[13] and Y_H/Y_D are summarized in Table 2.

Although the kinetic isotope effect in acetonitrile without magnesium ion could not be obtained, the value may be safely substituted by the one observed in 25% aqueous isopropanol.[7] This is partly supported by the facts that Y_H/Y_D's in both solvents have the same value and that the mechanism remains unchanged with the change in the polarity of solvent.[14] Thus, it is apparent that magnesium ion increases the value of k_H/k_D up to that of Y_H/Y_D. That is, the process of the initial electron-transfer is the major part of the rate-determining step of the reaction[15] without magnesium ion, whereas the process of proton-transfer becomes rate-determining step when magnesium ion exists in the reaction system. The catalytic activity of magnesium ion on the electron-transfer process has been proved by the observation described above.

In this connection, it is interesting to point out that appreciable kinetic

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

1, $10^2 M$	$Mg(ClO_4)_2$, $10^2 M$	$10^3 k_{obs}$, min^{-1}	$10^2 k_2$, $M^{-1}min^{-1}$ [b]
0.00	2.00	0.506	——
2.02	2.00	1.76	6.20
4.50	2.00	3.27	6.14
6.40	1.00	4.50	6.24
6.40	2.00	4.60	6.40
6.40	4.04	4.52	6.27
6.40	6.93	4.52	6.27
7.82	2.00	5.16	5.95
9.04	2.00	5.90	5.97
10.20	2.00	6.89	6.26

[a] [PNAH] = $1.00 \times 10^{-4} M$. Errors in rate constants were estimated to be ±3%.
[b] $k_2 = (k_{obs} - k_{dec})/[1]$, where k_{dec} is the rate constant at [1] = 0 M.

TABLE 2. Kinetic Isotope Effect (k_H/k_D) and Isotopic Ratio (Y_H/Y_D) in the Reduction of α,α,α-Trifluoroacetophenone with PNAH at 50°C

PNAH	Mg^{++}	Solvent	k_H/k_D	Y_H/Y_D
4-d_1	-	25% aq-Pr^iOH	1.38 ± 0.11[a]	3.8 ± 0.3[a]
4,4'-d_2 [b]	+	CH_3CN	3.65 ± 0.15	——
4-d_1	+	CH_3CN	3.62 ± 0.15	3.44 ± 0.2
4-d_1	-	CH_3CN	——[c]	3.65 ± 0.2

[a] Values reported in ref. 7. [b] 81% purity. [c] The reaction was too slow to be followed kinetically.

isotope effect was observed in the reduction with an alcohol dehydrogenase,[16] which requires the cooperation of zinc ion, whereas the reduction with a lactate dehydrogenase, which does not require the cooperation of metal ion, did not give kinetic isotope effect.[17] The rate-determining step prior to the migration of (net) hydride was suggested for the latter reaction.[17]

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