Reduction by a Model of NAD(P)H. XV. Kinetics for the Reduction of Methyl Benzoylformate

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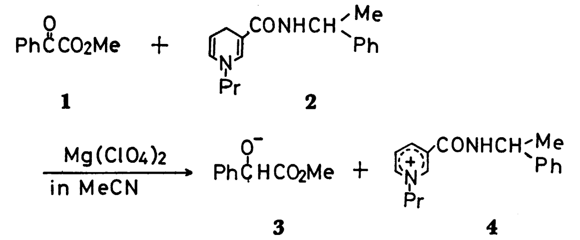
Kinetics for the reduction of methyl benzoylformate (**1**) with *N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide (**2**) in the presence of magnesium perchlorate in acetonitrile at 25 °C has been studied. The reaction follows first-order in **1**, first-order in **2**, and zero-order in magnesium ion when $[\mathbf{2}] \ll [\mathbf{1}]$, $[Mg(ClO_4)_2]$. When $[\mathbf{2}] = [Mg(ClO_4)_2] \ll [\mathbf{1}]$, the kinetics is best explained by Eqs. 6 and 7. The results indicate that **2** and magnesium ion form a complex, which reacts with **1** at the rate-determining step. It is concluded that magnesium ion activates **2** to promote the release of an electron.

It has been reported that biomimetic reduction of α-keto esters by a model of NAD(P)H takes place in acetonitrile in the presence of magnesium or zinc perchlorate.[1)] In addition to the promotion of the reduction, these metal salts also catalyze the asymmetric induction with a chiral model of NAD(P)H.[1)] Lithium perchlorate is effective, although the efficiency is much less than that of magnesium or zinc perchlorate, to promote the reduction, but the stereospecificity is absolutely absent with this lithium salt.[2)]

In a preceeding paper of this series,[2)] we proposed a mechanism of stereospecific magnesium ion-catalyzed reduction of methyl benzoylformate (**1**) with *N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide (**2**), where the importance of the initial formation of a complex between **2** and magnesium ion was suggested.



However, the existence of the complex prior to the reduction of **1** remained equivocal, and in order to confirm the previously proposed mechanism we studied the kinetics of the reduction.

Results and Discussion

Kinetics was followed at 25 °C by observing the decrease in the intensity of absorption at 354 nm. The absorption is characteristic of **2**. Pseudo-first-order rate constants, k_{obsd}, under various concentrations of **1** and of magnesium perchlorate are listed in Tables 1 and 2. In Tables 1 and 2 are also listed second-order rate constants, k_{calcd}, calculated by dividing k_{obsd} by the concentration of **1**. The result clearly indicates that the reaction kinetics is first-order in **1**, first-order in **2**, and zero-order in magnesium perchlorate under the conditions employed. The independency of the reaction rate from the concentration of magnesium perchlorate rules out the possibilities of initial formation of a complex between **1** and magnesium ion and of termolecular reaction with free reagents.

TABLE 1. DEPENDENCE OF THE RATE ON THE CONCENTRATION OF METHYL BENZOYLFORMATE

$[\mathbf{2}] \times 10^4$, M	$[Mg(ClO_4)_2] \times 10^3$, M	$[\mathbf{1}] \times 10^3$, M	$k_{obsd} \times 10^2$, min^{-1}	k_{calcd}, $M^{-1} min^{-1}$
2.00	5.89	5.90	3.84±0.15	6.51×0.30
1.99	12.05	6.11	4.79±0.18	6.75±0.30
2.00	5.96	7.41	5.14±0.20	6.94±0.31
1.99	6.03	12.21	8.26±0.31	6.76±0.30
2.00	5.99	13.61	9.62±0.37	7.06±0.31
2.00	5.99	15.03	10.82±0.40	7.20±0.33
2.00	6.01	16.52	11.82±0.45	7.15±0.31

TABLE 2. DEPENDENCE OF THE RATE ON THE CONCENTRATION OF MAGNESIUM PERCHLORATE

$[\mathbf{2}] \times 10^4$, M	$[Mg(ClO_4)_2] \times 10^3$, M	$[\mathbf{1}] \times 10^3$, M	$k_{obsd} \times 10^2$, min^{-1}	k_{calcd}, $M^{-1} min^{-1}$
2.00	3.91	11.92	8.16±0.30	6.84±0.31
2.00	6.06	11.74	7.86±0.30	6.70±0.30
1.99	6.03	12.21	8.26±0.31	6.76±0.30
2.00	11.91	11.92	8.53±0.31	7.15±0.31
2.00	23.81	12.34	8.36±0.31	6.77±0.30
2.00	35.70	12.40	8.00±0.30	6.45±0.30

It may be safely assumed that the first dissociation of magnesium perchlorate is practically complete in acetonitrile under the conditions where the concentrations of the salt are 10^{-2}—10^{-3} M.[3,4)] Thus, the present result is best interpreted, in agreement with the previously suggested mechanism, with the following reaction scheme:

$$Mg(ClO_4)_2 \underset{}{\overset{K_1}{\rightleftharpoons}} Mg(ClO_4)^+ + ClO_4^-$$

$$Mg(ClO_4)^+ + \mathbf{2} \overset{K_2}{\rightleftharpoons} \mathbf{2}\cdot Mg(ClO_4)^+$$

$$\mathbf{2}\cdot Mg(ClO_4)^+ + \mathbf{1} \xrightarrow{k_3} \mathbf{3}\cdot Mg^+ + \mathbf{4}\cdot ClO_4^-$$

It should be noted that the absorption at about 354 nm is not affected appreciably by the presence of magnesium perchlorate.[2)] That is, what we can observe by measuring the intensity of this absorption is the sum of concentrations of free and complexed **2**. This is an important point, because otherwise the observed kinetics does not predict the above scheme.

The validity of the proposed scheme can be tested in another way: when initial concentrations of **2** and magnesium perchlorate are set to be equal, Eq. 1 holds because the equilibrium constant K_1 has been assumed to be very large:

$$[\mathbf{2}]_T = [\mathrm{Mg(ClO_4)^+}]_T, \tag{1}$$

where the subscript T denotes the sum of concentrations of free and complexed species.

Since

$$\begin{aligned} K_2 &= [\mathbf{2}\cdot\mathrm{Mg(ClO_4)^+}]/[\mathrm{Mg(ClO_4)^+}][\mathbf{2}] \\ &= [\mathbf{2}\cdot\mathrm{Mg(ClO_4)^+}]/[\mathbf{2}]^2, \end{aligned} \tag{2}$$

therefore

$$[\mathbf{2}]_T = [\mathbf{2}] + K_2[\mathbf{2}]^2. \tag{3}$$

When Y is defined by Eq. 4

$$Y = (1 + 4K_2[\mathbf{2}]_T)^{1/2} \tag{4}$$

the kinetic expression according to the proposed reaction scheme can be written as in Eq. 5,

$$\begin{aligned} -\mathrm{d}[\mathbf{2}]_T/\mathrm{d}t &= k_3[\mathbf{2}\cdot\mathrm{Mg(ClO_4)^+}][\mathbf{1}] \\ &= K_2k_3[\mathbf{2}]^2[\mathbf{1}] \\ &= k_3[\mathbf{1}](Y-1)^2/4K_2. \end{aligned} \tag{5}$$

Finally, we obtain Eqs. 6 and 7 under the conditions of $[\mathbf{2}]=[\mathrm{Mg(ClO_4)_2}]\ll[\mathbf{1}]$

$$(Y-1)^{-1} - \ln(Y-1) = k_3[\mathbf{1}]t/2 + C, \tag{6}$$

$$C = (Y_0-1)^{-1} - \ln(Y_0-1), \tag{7}$$

where Y_0 is the value of Y at $t=0$.

The values for K_2 and k_3 were obtained by computer-assisted iteration with the Newton's method[5] and the result is summarized in Table 3. The excellent agreement between the values for k_3 and k_{calcd} proves the validity of the proposed reaction scheme. The value for K_2 also agrees with the idea that practically all molecules of **2** in the reaction system are complexed by magnesium ion under the conditions with which the pseudo-first-order kinetics was studied.

Hughes and Prince reported that the rate of reduction of 2-pyridinecarbaldehyde exibits a half-order dependence on total metal salt concentration.[6] Indeed, our kinetic result obtained under the conditions of $[\mathbf{2}]=[\mathrm{Mg(ClO_4)_2}]\ll[\mathbf{1}]$ is very well processed by a two-third order dependence on total concentration of **2**. Therefore, it may provide another possibility that the rate depends on the first-order in **2** and a half-order in magnesium perchlorate. However, such a kinetics comes out only when the dissociation constant of magnesium perchlorate in acetonitrile is very small. If this were the case, the kinetics under the conditions of $[\mathbf{2}]<[\mathrm{Mg(ClO_4)_2}]\ll[\mathbf{1}]$ should deviate from the first-order in **2** in contrast to the observed result. Thus, the assumption that K_1 has a large value has been proved to be valid.

Table 3. Computed values for rate and equilibrium constants

$[\mathbf{2}]\times10^4$, M	$[\mathrm{Mg(ClO_4)_2}]$ $\times10^4$, M	$[\mathbf{1}]\times10^3$, M	k_3, $\mathrm{M^{-1}\,min^{-1}}$	$K_2\times10^{-3}$, $\mathrm{M^{-1}}$
1.99	1.99	24.00	6.91	1.98
1.99	1.99	24.15	6.86	1.82
1.99	2.00	23.82	6.99	1.65
1.99	1.99	12.08	6.96	2.03

The kinetics has revealed that the complex, $\mathbf{2}\cdot\mathrm{Mg(ClO_4)^+}$, is the reacting species and the role of magnesium ion is not only to activate the substrate but also to activate the model compound.[7] In this way, **2** releases an electron, a proton, and an electron, successively. This conclusion is different from that proposed by Gase and his coworkers, who assigned free **2** as a reacting species.[8]

Lithium perchlorate gave a quite complex kinetics which could not be interpreted. The reaction rate depended on the concentration of lithium ion even in the region of 15×10^{-3} M against 2×10^{-4} molar concentration of **2**. The result may probably due to the formation of various types of aggregates in concordance with the idea previously proposed in a simplified form.[2]

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Experimental

Materials. Acetonitrile was distilled once on phosphorus pentaoxide and kept over molecular sieves 4A. Magnesium and lithium perchlorates were dried at 120 °C *in vacuo* for 5 h and used immediately. Preparations of methyl benzoylformate and *N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide were described previously.[9]

Procedure. Acetonitrile was flushed with dry argon prior to the use. In a glove-box filled with dry argon, solutions for kinetic studies were prepared and placed in a UV-cell (1 cm) equipped with a silicone-rubber stopper. Kinetics was followed spectrophotometrically with a Union Giken SM-401 spectrophotometer, the cell-compartment of which was filled with dry argon and kept at 25.0+0.1 °C. The order of incubation of reagents did not affect the kinetics.

Kinetics. In the presence of a large excess of magnesium perchlorate, the reactions gave good first-order plots over three half-lives ($r>0.9997$). In the presence of a small amount of magnesium perchlorate, the kinetics over 75% conversion of the reaction was processed well with Eqs. 6 and 7. Iterations of K_2 and k_3 by a FACOM 230 OS2/VS with a FORTRAN IV program gave constants which reproduced experimentally obtained plots exactly.

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