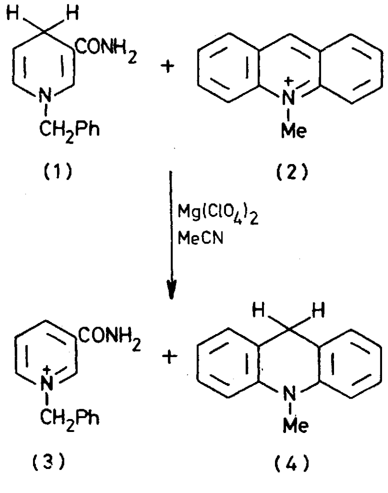
# Influence of $Mg^{2+}$ Ion on the Reduction of *N*-Methylacridinium Ion with 1,4-Dihydronicotinamide

By SEIJI SHINKAI,* TOYOKO IDE, HISATAKE HAMADA, OSAMU MANABE, and TOYOKI KUNITAKE
(*Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki* 852, *Japan, and Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka* 812, *Japan*)

*Summary* The reaction of *N*-benzyl-1,4-dihydronicotinamide and *N*-methylacridinium ion in the presence of $Mg^{2+}$ gives a normal secondary isotope effect ($k_H/k_H' = 0{\cdot}98 \pm 0{\cdot}04$) and an identical value (3·7) for the primary isotope effect ($k_H/k_D$) and the isotopic partitioning ratio.

ANALYSIS of isotope effects in non-enzymatic reductions with dihydronicotinamide has been a controversial question since Steffens and Chipman[1] and Sigman *et al.*[2,3] proposed that a kinetically detectable intermediate exists during reductions with dihydronicotinamide on the basis of the abnormal secondary isotope effect ($k_H/k_H'$ 0·73—0·74). This intermediate was presumed in some cases to be a charge-transfer-type complex.[4,5]† It was thus assumed that dihydronicotinamide releases an electron prior to proton transfer, and the hydride transfer mechanism was rejected.[5] The two-step mechanism is not incompatible with the fact that dihydronicotinamide is capable of acting as an electron donor under mild condition.[6,7] Here, we report that a charge-transfer complex is not formed to any great extent with *N*-methylacridinium ion (**2**) and the *N*-benzyl-1,4-dihydronicotinamide (**1**)–$Mg^{2+}$ complex[5] and that the reaction gives a normal secondary isotope effect (*ca.* 1·0) and an identical value for the isotopic partitioning ratio and the primary isotope effect.

The reactions were carried out at 30 ± 0·1 °C in acetonitrile. The absorption spectrum of (**1**) was significantly affected by added $Mg^{2+}$ (red shift), while that of (**2**) was not.‡ The reaction rate was retarded with increasing $Mg^{2+}$ concentration and gradually reached a constant value. The largest rate decrease was 6 fold. Since the rate saturation is observed at $[Mg^{2+}]/[(\mathbf{1})] = ca.\ 1{\cdot}0$, formation of a 1 : 1 complex is presumed. The absorption of the charge-transfer-type complex between (**1**) and (**2**) (*ca.* 600 nm)[4] almost disappeared at $[Mg^{2+}]/[(\mathbf{1})] = 1{\cdot}2$ (<10% of absorption in the absence of $Mg^{2+}$). These results indicate strongly that the interaction of the (**1**)–$Mg^{2+}$ complex (cationic species) with (**2**) is suppressed owing to the repulsion between the like charges. A similar rate retardation by metal ions is known in the reduction of Malachite Green with dihydronicotinamide.[8] However, the reduction of 3-methyl-10-butylisoalloxazine and 3-methyl-10-butyl-5-deazaisoalloxazine (neutral species) with dihydronicotinamide was hardly affected by added $Mg^{2+}$ ion.



The calculated second-order rate constants ($k_r$ and $k_r^d$) for the reduction of (**2**) by (**1**) and 4-deuteriodihydronicotinamide [4-$^2H_1$]-(**1**) are summarized in the Table. The kinetic isotope effects obtained in the absence of $Mg^{2+}$ are quite different from those calculated based on a reaction mechanism involving simple one-step hydrogen transfer [*i.e.*, the secondary isotope effect $k_H/k_H' = 1{\cdot}0$ and the

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† The possibility that the charge-transfer-type complex is a nonproductive intermediate cannot be excluded (ref. 4).

‡ For details of the kinetic measurements see ref. 2.

**TABLE.** Kinetic and product analysis data for reactions of *N*-benzyl-1,4-dihydronicotinamide (**1**) and $[4\text{-}^2H_1]$-(**1**) with *N*-methylacridinium ion (**2**).[a]

| | Additive | |
|---|---|---|
| | None | $[Mg(ClO_4)_2]$ $(1{\cdot}20 \times 10^{-3}M)$ |
| $k_r/(l\ mol^{-1}\ s^{-1})$ | $72{\cdot}3 \pm 0{\cdot}3$ | $16{\cdot}7 \pm 0{\cdot}1$ |
| $k_r^d/(l\ mol^{-1}\ s^{-1})$ | $63{\cdot}9 \pm 0{\cdot}4$ | $10{\cdot}8 \pm 0{\cdot}2$ |
| $k_r/k_r^d$ | $1{\cdot}13 \pm 0{\cdot}06$ | $1{\cdot}55 \pm 0{\cdot}04$ |
| (**4**)-H/(**4**)-D | $4{\cdot}0 \pm 0{\cdot}2$ | $3{\cdot}7 \pm 0{\cdot}2$ |
| $k_H/k_H'$ | $0{\cdot}71 \pm 0{\cdot}03$ | $0{\cdot}98 \pm 0{\cdot}04$ |
| $k_H/k_D$ | $2{\cdot}76 \pm 0{\cdot}15$ | $3{\cdot}70 \pm 0{\cdot}18$ |

[a] $[(\mathbf{1})] = 1{\cdot}00 \times 10^{-3}M$; $[(\mathbf{2})] = 4{\cdot}0 \times 10^{-5}M$.

primary isotope effect $k_H/k_D$ equals the isotopic partitioning ratio (**4**)-H/(**4**)-D].[1]§ In the presence of $Mg^{2+}$ ($[Mg^{2+}]/[(\mathbf{1})$ or $^2H_1$-$(\mathbf{1})] = 1{\cdot}2$), however, these values are in fair agreement with the values proposed for simple one-step hydrogen transfer.¶ It is thus evident that added $Mg^{2+}$ ion changes the reaction path to a simple one-step-type reaction from a reaction of the type (**1**) + (**2**) $\rightleftharpoons$ intermediate $\rightarrow$ products.

In conclusion, the present study demonstrates that, when the formation of the charge-transfer complex is suppressed, the isotope effects become compatible with those proposed for a simple bimolecular reaction. Therefore, the anomalous isotope effects in the absence of $Mg^{2+}$ must be caused by the formation of an intermediate during the reduction with dihydronicotinamide.

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§ For the method of calculation see refs. 1 and 2.

¶ As a related example, Ohno *et al.* found that the reaction of (**1**)—$Mg^{2+}$ and methyl benzoylformate gives similar value for $k_H/k_D$ and product-H/product-D: A. Ohno, H. Yamamoto, S. Oka, and Y. Ohnishi, *Bull. Chem. Soc. Japan*, submitted for publication.

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