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REDUCTION OF N-METHYLACRIDINIUM ION BY 3-AMINOCARBONYL-N-BENZYL-1,4-DIHYDROQUINOLINE: SUPPORTING EVIDENCE FOR THE MULTI-STEP MECHANISM OF THE NADH MODEL REDUCTION

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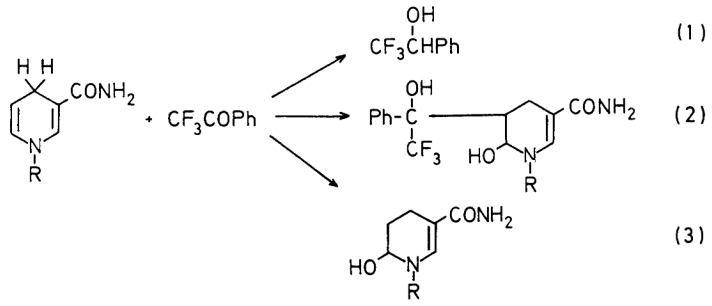
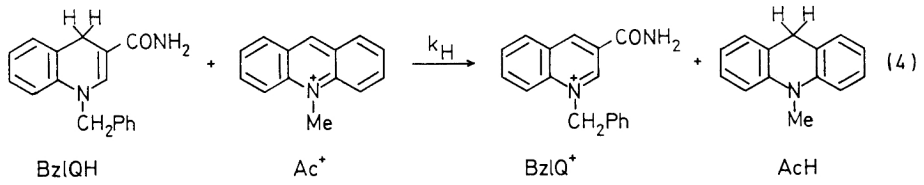
The reduction of N-methylacridinium ion by 3-aminocarbonyl-N-benzyl-1,4-dihydroquinoline showed the isotope effect discrepancy. The result supports the multi-step hydrogen transfer mechanism.

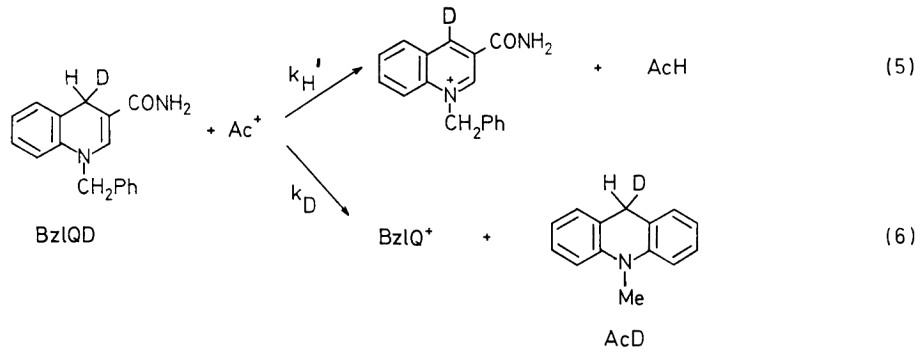
Analysis of isotope effects observed in dihydronicotinamide reductions has been a controversial question since Steffens and Chipman[1] and Sigman et al.[2] proposed that a kinetically detectable intermediate exists during reductions with dihydronicotinamide on the basis of the abnormal secondary isotope effect (k_H/k_H' = 0.73-0.74). In some cases, the intermediate is presumed to be a charge-transfer complex.[3,4] The primary isotope effects (k_H/k_D) in these abnormal systems are usually in the range 3.8-5.4,[5] suggesting that the hydrogen transfer may be involved only partially in the rate-determing step. On the other hand, when (i) the primary isotope effects are extremely large (~13.3) and (ii) divalent metal cations are added in the reaction systems, the secondary isotope effects (k_H/k_H') become rather normal (1.0-1.1).[6-8]

Recently, van Eikeren et al.[5,9] proposed for the dihydronicotinamide reduction of trifluoroacetophenone that the discrepancy in the isotope effect is due to concomitant nonproductive reactions such as the reversible formation of a covalent adduct (Eq. 2) and the acid-catalyzed decomposition of the dihydronicotinamide (Eq. 3). They concluded that the discrepancy between isotope effects determined by kinetics and by partitioning experiments, without "product analysis", is thus not valid evidence for the multi-step mechanism.[9] They consider that the discrepancy observed for the reduction of N-methylacridinium ion (Ac^+) by dihydronicotinamides[2,3] may be also due to the formation of a covalent adduct at the 9-position of Ac^+.[10]



These nonproductive reactions are all associated with the nucleophilic nature of the enamine moiety of 1,4-dihydronicotinamide.[11] We recently synthesized an acid-stable NADH model compound, 3-aminocarbonyl-N-benzyl-1,4-dihydroquinoline (BzlQH).[12] Since the nucleophilic, acid-sensitive 5,6-double bond is involved in the aromatic ring, the nonproductive reactions proposed by van Eikeren et al.[5] are hardly conceivable. Based on the product analysis and the kinetic measurements, we estimated the isotope effect for the net redox reaction between Ac^+ and BzlQH (or BzlQD: monodeuterated BzlQH).[13]





In the first place, we carried out the product analysis in order to rule out the possibility of the nonproductive reactions (30°C, acetonitrile, [BzlQH] = 2.00×10^{-3} M, [Ac^+] = 1.00×10^{-3} M). The yields of N-methylacridan (AcH) and $BzlQ^+$, which were determined by high-pressure LC, were saturated under the aerobic conditions at about 90% reaction and two unknown products were detected. On the other hand, the reaction under the anaerobic (N_2) conditions reached 100% within 2 h, indicating the anaerobic reaction between Ac^+ and BzlQH to be quantitative without the side-reactions such as the adduct formation and the decomposition.

The kinetic and partitioning data are summarized in Table 1. Importantly, the second-order rate constants (k_r and k_r^d for BzlQH and BzlQD, respectively) under the aerobic conditions are somewhat smaller than the anaerobic second-order rate constants. We thus used the anaerobic rate constants for the following calculation.[14] Examination of Table 1 reveals that the secondary isotope effect ($k_H/k_H' = 0.75$) calculated by assuming simple one-step hydrogen transfer is significantly smaller than unity. If one assumes $k_H/k_H' = 1.0$ as usually observed for one-step hydrogen transfer, one obtains the primary isotope effect of $k_H/k_D = 2.0$. Clearly, this value

Table 1 Kinetic and product analysis data[a)]

	Anaerobic	Aerobic
k_r (M^{-1} s^{-1})	16.8 ± 0.3	15.7 ± 0.5
k_r^D (M^{-1} s^{-1})	12.6 ± 0.1	11.5 ± 0.3
Y^H / Y^D	7.6 ± 0.3	
k_H / k_H'	0.75 ± 0.02	
k_H / k_D	2.0 ± 0.2	

a) 30°C in acetonitrile. Product analysis: $[BzlQD] = 1.00 \times 10^{-3}$ M, $[Ac^+] = 2.00 \times 10^{-3}$ M, 3 h; kinetic measurements: [BzlQH(or BzlQD)] = 1.44×10^{-3} M, $[Ac^+] = 4.49 \times 10^{-5}$ M.

is smaller than the ratio of isotope partitioning ($Y^H/Y^D = 7.6$). These observations allow us to conclude that the isotope discrepancy does exist in the reaction of Ac^+ and BzlQH.

Very recently, Ohno et al.[15)] examined the 1-N-substituent effect on the dihydronicotinamide reduction of Ac^+. They found that the plot of k_H/k_D vs. Hammett's σ for the substituents on 1-N-phenyl group provides a maximum (at methyl group) and the discrepancy between k_H/k_D and Y^H/Y^D becomes larger with increasing electron-withdrawing nature of the substituent. It is known that the "basicity" of 1-N of BzlQH is relatively weak because of the conjugation with the benzene ring.[12)] Therefore, the kinetic situation for BzlQH may be comparable with that for the dihydronicotinamide with the strong electron-withdrawing 1-N-substituent.

In conclusion, the present results support the multi-step hydrogen transfer mechanism (at least for the combination of BzlQH and Ac^+). The effect of the aerobic conditions observed suggests that the reaction would involve some radical intermediate.

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