Effect of Magnesium Ion distinguishing between One-step Hydrogen- and Electron-transfer Mechanisms for the Reduction of Stable Neutral Radicals by NADH Analogues

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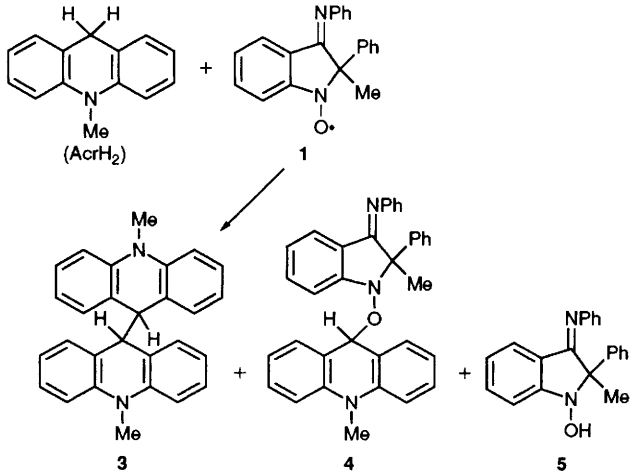
Hydrogen transfer from NADH analogues to indolinone and phenyliminoindolinone aminoxyl radicals proceeds *via* a one-step hydrogen-transfer process, in which no catalytic effect of Mg^{2+} has been observed, while the hydrogen transfer to 1,1-diphenyl-2-picrylhydrazyl radical proceeds *via* electron transfer from NADH analogues to the radical, which is catalyzed significantly by the presence of Mg^{2+} in MeCN.

Dihydronicotinamide adenine dinucleotide (NADH) and analogues act as the source of two electrons and a proton, thus formally transferring a hydride ion to a suitable substrate.[1] Although the mechanisms of the hydride-transfer reactions of NADH analogues have been studied extensively,[2,3] little is known about the mechanisms of hydrogen-transfer reactions from NADH analogues to radical species. There are two possibilities in the mechanisms of hydrogen-transfer reactions, *i.e.*, a one-step hydrogen transfer or electron transfer followed by proton transfer.[3–5] We report herein that the effect of Mg^{2+} provides a reliable criterion for distinguishing between the one-step hydrogen-transfer and electron-transfer mechanisms.

Indolinone aminoxyl radicals, 1,2-dihydro-2-methyl-2-phenyl-3-phenylimino-3*H*-indol-1-oxyl (**1**) and 1,2-dihydro-3-oxo-2,2-diphenyl-3*H*-indol-1-oxyl (**2**) are stable in MeCN.[6] The reaction of **1** with an NADH analogue, 10-methyl-9,10-dihydroacridine ($AcrH_2$) yields 10,10′-dimethyl-9,9′,10,10′-tetrahydro-9,9′-biacridine (**3**), the adduct (**4**) and the corresponding *N*-hydroxide (**5**) (Scheme 1). The products were identified by the ^1H NMR spectra as well as TLC using the authentic samples for comparison.[7] The isolated yield of dimer (**3**) was 65%. Likewise the reactions of 1-benzyl-1,4-dihydronicotinamide (BNAH) with **1** and **2** as well as the reaction of $AcrH_2$ with **2** yield the dimer, the adduct and the corresponding *N*-hydroxide. On the other hand, the reaction of $AcrH_2$ with 1,1-diphenyl-2-picrylhydrazyl hydrate



Scheme 1

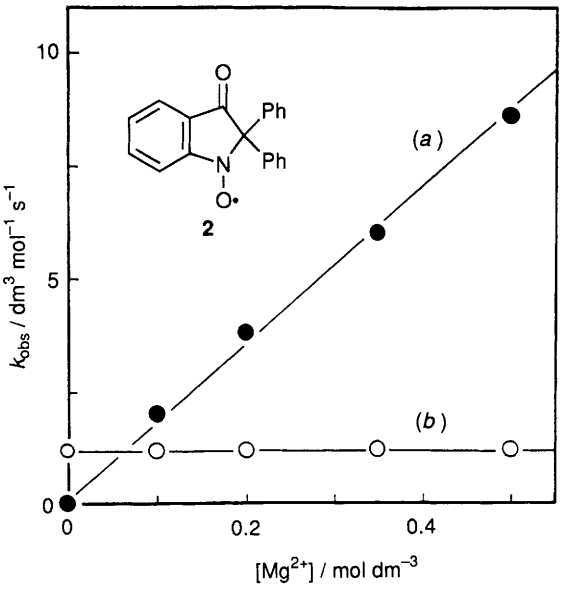


Fig. 1 Dependence of k_{obs} on [Mg^{2+}] for (*a*) electron transfer from **3** (●) to **2** and (*b*) hydrogen transfer from $AcrH_2$ (○) to **2** in the presence of $Mg(ClO_4)_2$ in deaerated MeCN at 323 K

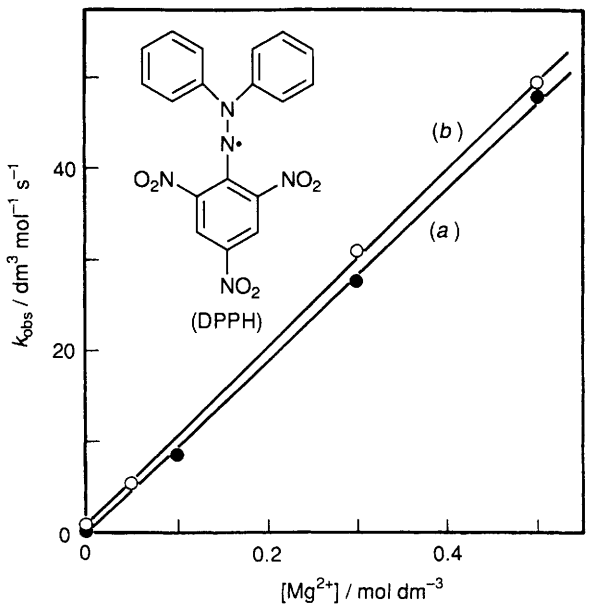


Fig. 2 Dependence of k_{obs} on [Mg^{2+}] for (*a*) electron transfer from **3** (●) to DPPH• in deaerated MeCN at 313 K and (*b*) hydrogen transfer from $AcrH_2$ (○) to DPPH• in the presence of $Mg(ClO_4)_2$ in deaerated MeCN at 298 K

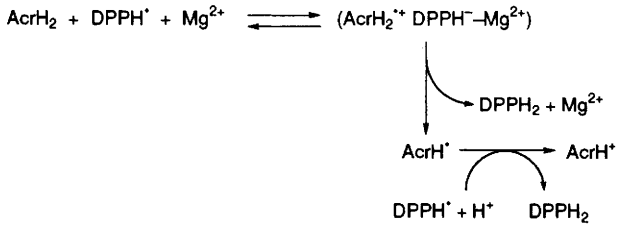
$$AcrH_2 + 2DPPH^{\bullet} + H^+ \longrightarrow AcrH^+ + 2DPPH_2$$

Scheme 2

(DPPH•) yields 10-methylacridinium ion ($AcrH^+$) and 1,1-diphenyl-2-picrylhydrazine ($DPPH_2$) (Scheme 2).

The rates of reactions of $AcrH_2$ with **1**, **2** and DPPH• were determined by monitoring the disappearance of the absorbance due to the radicals (**1**: λ_{max} = 430 nm, ε_{max} = 1.7 × 10^3 dm^3 mol^{-1} cm^{-1}; **2**: λ_{max} = 428 nm, ε_{max} = 1.1 × 10^3 dm^3 mol^{-1} cm^{-1}; DPPH•: λ_{max} = 512 nm, ε_{max} = 1.5 × 10^4 dm^3 mol^{-1} cm^{-1}). The rates obeyed second-order kinetics showing a first-order dependence on each reactant concentration, indicating that the initial hydrogen transfer from NADH analogues to the radicals is the rate-determining step.

We have recently reported that the dimer (**3**) acts as a novel outer-sphere electron-transfer organic reagent rather than a hydrogen donor.[8] No electron transfer from **3** to **1** or **2** has occurred, consistent with the larger one-electron oxidation potential of **3** (0.62 V *vs.* SCE)[8] than the one-electron reduction potentials of **1** (−0.66 V) and **2** (−0.87 V), which were determined by cyclic voltammetry. When $Mg(ClO_4)_2$ is added to the **3**–**1** (or **2**) system, however, electron transfer from **3** to **1** occurs to yield $AcrH^+$ and the *N*-hydroxide anion–Mg^{2+} complex. The observed second-order rate constant (k_{obs}) increases linearly with an increase in [Mg^{2+}] as shown in Fig. 1(*a*). Although no interaction between Mg^{2+} and **1** or **2** has been detected in the electronic spectra in the presence of Mg^{2+}, the coordination of Mg^{2+} to the one-electron reduced species may stabilize the product, resulting in the acceleration of electron transfer.[3] If the hydrogen transfer from $AcrH_2$ to the aminoxyl radical involves such an electron-transfer process as the rate-determining step, the rate of hydrogen transfer would also be accelerated by the presence of Mg^{2+}. The effect of Mg^{2+} on the rates of hydrogen transfer from $ArcH_2$ to **1** is also shown in Fig. 1(*b*), where no effect of Mg^{2+} on the k_{obs} values is observed, demonstrating sharp contrast with the case of the electron-transfer reaction from **3** to **1** [Fig. 1(*a*)]. Thus, there may be no contribution of electron transfer from $AcrH_2$ to the aminoxyl radical in the hydrogen-transfer reaction, which may thereby proceed *via* a one-step hydrogen-transfer process. In fact a large primary kinetic isotope effect was observed (k_H/k_D = 21 at 323 K)



Scheme 3

when $AcrH_2$ was replaced by the 9,9-dideuteriated analogue ($AcrD_2$). The direct transfer of hydrogen atom from $AcrH_2$ to the aminoxyl radical gives acridinyl radical (AcrH•) and the *N*-hydroxide. The homo-coupling of AcrH• and the cross-coupling of AcrH• with the aminoxyl radical yielded the dimer **3** and the adduct **4**, respectively.

On the other hand, electron transfer from **3** to DPPH• is also catalysed by the presence of Mg^{2+} as shown in Fig. 2(*a*). In contrast with the case of aminoxyl radicals, Mg^{2+} also accelerates significantly the rate of hydrogen transfer from $AcrH_2$ to DPPH• as shown in Fig. 2(*b*). Thus, the hydrogen transfer may proceed *via* electron transfer from $AcrH_2$ to DPPH•, which is accelerated by the presence of Mg^{2+}, followed by proton transfer from $AcrH_2^{\bullet+}$ to $DPPH^-$ to yield $DPPH_2$ (Scheme 3). The resulting acridinyl radical (AcrH•) is a much stronger reductant than $AcrH_2$, judging from the negative oxidation potential (−0.43 V)[9] as compared to that of $AcrH_2$ (0.80 V),[9] and thereby AcrH• can readily transfer an electron to another DPPH• molecule to yield $AcrH^+$ (Scheme 3). The primary kinetic isotope effect determined as k_H/k_D = 3.0 at 323 K, which may be ascribed to the proton transfer from $AcrH_2^{\bullet+}$ to $DPPH^-$ in Scheme 3, is significantly smaller than that in the direct hydrogen-transfer process from $AcrH_2$ to the aminoxyl radical (see above). The difference in the mechanism of hydrogen-transfer reactions of aminoxyl radicals and DPPH• may be ascribed to the difference in the one-electron reduction potentials. The electron-transfer process is much favoured in the case of DPPH• which has the positive one-electron reduction potential (0.24 V) as compared to the negative one-electron reduction potentials of aminoxyl radicals (see above). The significant steric effect of

the bulky substituents of DPPH$^{\bullet}$ may also contribute to favour the electron-transfer pathway, since no significant interaction is required for the electron-transfer process as compared to an alternative direct hydrogen-transfer process which requires the close contact of the reactants.

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