

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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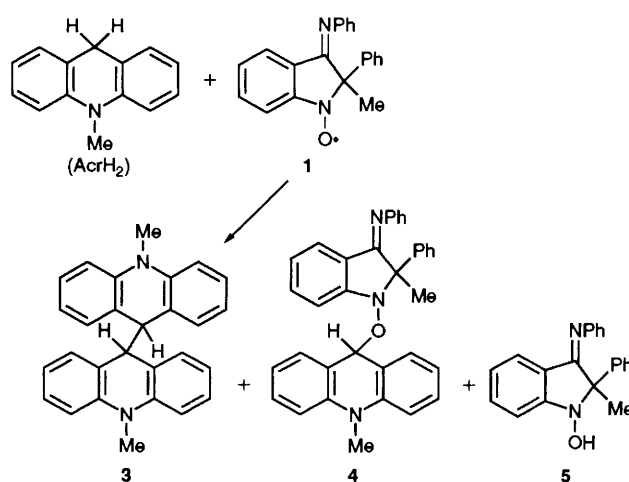
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Hydrogen transfer from NADH analogues to indolinone and phenyliminoindolinone aminoxy radicals proceeds *via* a one-step hydrogen-transfer process, in which no catalytic effect of Mg²⁺ has been observed, while the hydrogen transfer to 1,1-diphenyl-2-picrylhydrazyl radical proceeds *via* electron transfer from NADH analogues to the radical, which is catalyzed significantly by the presence of Mg²⁺ in MeCN.

Dihyronicotinamide 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 Mg²⁺ provides a reliable criterion for distinguishing between the one-step hydrogen-transfer and electron-transfer mechanisms.

Indolinone aminoxy 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 (AcrH₂) 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-dihyronicotinamide (BNAH) with **1** and **2** as well as the

reaction of AcrH₂ with **2** yield the dimer, the adduct and the corresponding *N*-hydroxide. On the other hand, the reaction of AcrH₂ with 1,1-diphenyl-2-picrylhydrazyl hydrate



Scheme 1

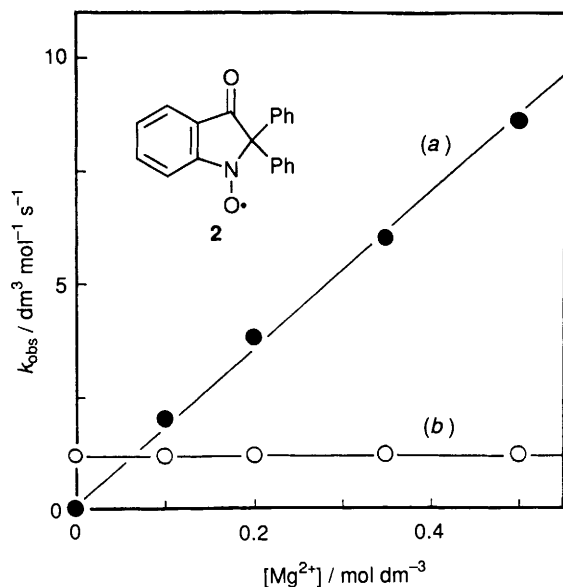
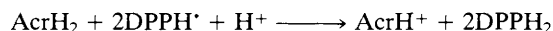


Fig. 1 Dependence of k_{obs} on $[\text{Mg}^{2+}]$ for (a) electron transfer from **3** (●) to **2** and (b) hydrogen transfer from AcrH_2 (○) to **2** in the presence of $\text{Mg}(\text{ClO}_4)_2$ in deaerated MeCN at 323 K



Scheme 2

(DPPH^{\cdot}) 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^{\cdot} were determined by monitoring the disappearance of the absorbance due to the radicals (**1**: $\lambda_{\text{max}} = 430 \text{ nm}$, $\epsilon_{\text{max}} = 1.7 \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$; **2**: $\lambda_{\text{max}} = 428 \text{ nm}$, $\epsilon_{\text{max}} = 1.1 \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$; DPPH^{\cdot} : $\lambda_{\text{max}} = 512 \text{ nm}$, $\epsilon_{\text{max}} = 1.5 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$). 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 $\text{Mg}(\text{ClO}_4)_2$ 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 $[\text{Mg}^{2+}]$ 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 AcrH_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 ($k_{\text{H}}/k_{\text{D}} = 21$ at 323 K)

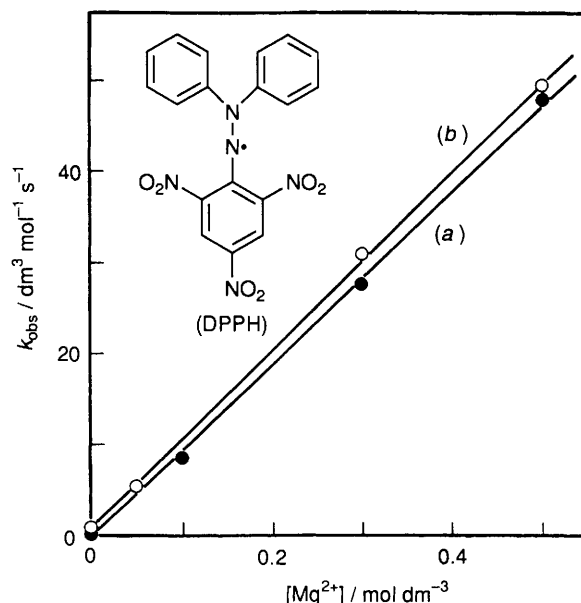
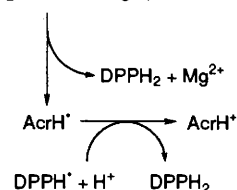


Fig. 2 Dependence of k_{obs} on $[\text{Mg}^{2+}]$ for (a) electron transfer from **3** (●) to DPPH^{\cdot} in deaerated MeCN at 313 K and (b) hydrogen transfer from AcrH_2 (○) to DPPH^{\cdot} in the presence of $\text{Mg}(\text{ClO}_4)_2$ in deaerated MeCN at 298 K



Scheme 3

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

On the other hand, electron transfer from **3** to DPPH^{\cdot} 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^{\cdot} as shown in Fig. 2(b). Thus, the hydrogen transfer may proceed *via* electron transfer from AcrH_2 to DPPH^{\cdot} , which is accelerated by the presence of Mg^{2+} , followed by proton transfer from $\text{AcrH}_2^{\cdot+}$ to DPPH^- to yield DPPH_2 (Scheme 3). The resulting acridinyl radical (AcrH^{\cdot}) 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^{\cdot} can readily transfer an electron to another DPPH^{\cdot} molecule to yield AcrH^+ (Scheme 3). The primary kinetic isotope effect determined as $k_{\text{H}}/k_{\text{D}} = 3.0$ at 323 K, which may be ascribed to the proton transfer from $\text{AcrH}_2^{\cdot+}$ 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^{\cdot} may be ascribed to the difference in the one-electron reduction potentials. The electron-transfer process is much favoured in the case of DPPH^{\cdot} 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[•] 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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