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Communications

Formation of Novel 1:1 Adducts Accompanied by Regioselective Hydride Transfer from Transition-Metal Hydrido Complexes to NAD(P) Models

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Summary: Important intermediates in regioslective hydride reduction of NAD(P) model compounds were detected by various spectroscopic methods. The metal hydrido complexes [Ru(tpy)(bpy)H]$^+$ and [Re(bpy)(CO)$_3$H] react with the NAD(P) models to give 1:1 adducts, which are cleaved to the 1,4-dihydro form of the models and the solvento complexes, quantitatively.

Oxidation of 1,4-dihydropyridine compounds with various substrates has been extensively studied to provide mechanistic insights into the biological oxidation of reduced pyridine nucleotide coenzymes NAD(P)H and to develop synthetic applications of the coenzymes and their model compounds.[1,2] In contrast, only a limited number of reports have appeared for the nonenzymic regioselective reduction of 1-substituted pyridinium cation derivatives by hydride donors, which can provide mechanistic information for the enzymic reduction of the coenzymes NAD(P).[1] Consequently, little has been known about the chemical details for the regioselective enzymic reduction of NAD(P), and also serious difficulties have emerged in the development of artificial systems mimicking the biological regioselective reduction of NAD(P) and of synthetic applications, e.g., asymmetric catalysts.[2]

Although some hydrido- and formylmetal complexes has been reported as rare reductants which can regioselectivity convert NAD(P) and the model compounds to the corresponding 1,4-dihydro form,[3] their mechanistic details are still unknown. Recently, the importance of interaction between the carbamoyl group of NAD(P) models and the metal center of a metal complex has been presumed on the basis of the different reactivities of the complex, with the NAD(P) models having different substituents at the 3-position.[3b,c] However, no

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(4) The reactions of the NAD(P) models with [Ru(tpy)(bpy)D]$^+$ and [Re(bpy)(CO)$_3$D] resulted in >95% deuterium incorporation on the 4-position of the 1,4-dihydropyridine ring of the adducts, even in the presence of excess H_2O. In contrast, in the reactions of the undeuterated metal hydrides in CD_3CN containing a few drops of D_2O, no deuterium incorporation in the dihydropyridine ring of the adducts occurred while deuterium was scrambled into the carbamoyl N−H bonds.

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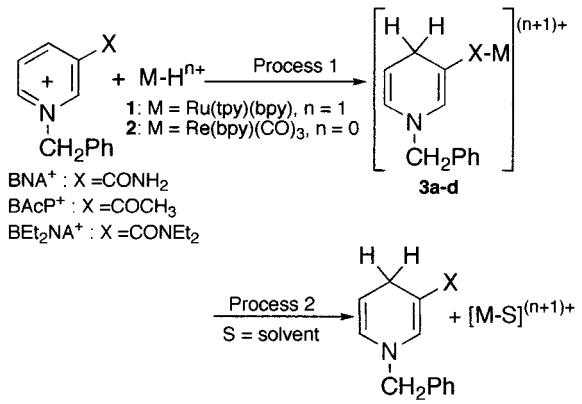
Scheme 1. Reaction of NAD(P) Models with Metal Hydrido Complexes[a]



[a] All of the counter anions are PF_6^-.

direct evidence for the presence of either intermediates or activated complexes have been reported so far.

We report here that NAD(P) models do form a novel type of relatively stable 1:1 adducts with metal hydrido complexes, followed by quantitative dissociation into the corresponding 1,4-dihydro form of the models and the solvento metal complexes (Scheme 1). The studies of the adduct formation process give important information about the regioselective hydride transfer to the 4-position of NAD(P) and the models.

When the PF_6^- salt of 1-benzyl-3-carbamoylpyridinium cation (BNA^+, a typical NAD(P) model compound) (15 μmol) was added to a 1 mL solution of the PF_6^- salt of $[Ru(tpy)(bpy)H]^+$ (**1**; tpy = 2,2′;6′,2″-terpyridine, bpy = 2,2′-bipyridine) (15 μmol) at room temperature, the 1:1 adduct (**3a**) was quantitatively formed (Process 1 in Scheme 1) and then underwent a relatively slow reaction to give 1,4-BNAH and the solvento complex in quantitative yield (Process 2 in Scheme 1). The observed first-order rate constant in the presence of 0.4 M water was 3.5×10^{-4} s^{-1} at 28 °C. It was confirmed that no positional isomers of 1,4-BNAH, i.e., 1,2- and 1,6-BNAH's, are involved at all in the reaction mixture. Isotope experiments using $[Ru(tpy)(bpy)D]^+$ clearly demonstrate that the hydride ligand of the metal hydrides specifically transfers to the 4-position of the NAD(P) models, a regioslective hydride transfer reminiscent of the enzymic reactions.[4]

The structure of **3a** was indicated by electrospray ionization mass analysis, which showed a main ion peak corresponding to $[\mathbf{1} + BNA^+]^{2+}$ (m/z 352) with a small peak of $[\mathbf{1} + BNA^+ - H^+]^+$ (m/z 704). Moreover, ^{1}H NMR spectra of **3a** showed a resonance assignable to a 1,4-dihydropyridine structure. The chemical shifts for the protons (Figure 1) on both the 4-position (2.53 ppm) and the 2-position (6.14 ppm) of the dihydropyridine ring of the adduct were shifted downfield by 0.52 and 0.81 ppm compared with free 1,4-BNAH, respectively, while the other protons on the dihydropyridine ring, which are farther from the carbamoyl group, were shifted down only by 0.02−0.14 ppm. The infrared absorption for ν_{CO} of the carbamoyl group was observed at 1530 cm^{-1}, lower by 49 cm^{-1} compared with that of 1,4-BNAH.[6] It is therefore strongly indicated that the carbamoyl group of the 1,4-BNAH moiety coordinates to the Ru^{II} center in **3a**.[7]

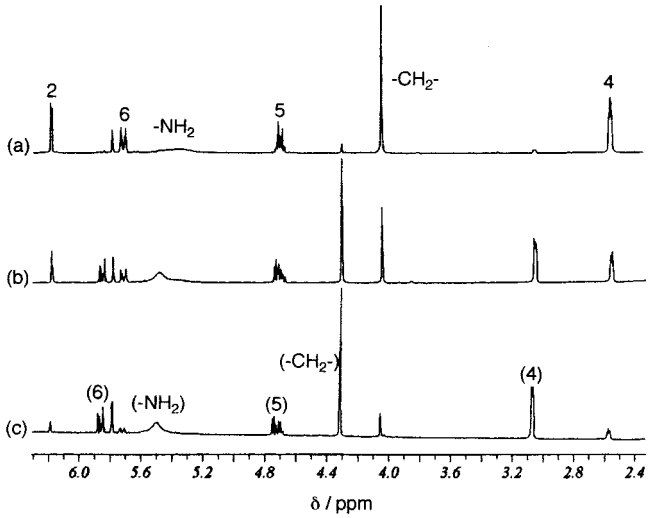


Figure 1. Proton NMR spectral change of an CD_3CN solution containing **1** (15 μmol) after addition of $BNA^+PF_6^-$ (15 μmol): (a) within 10 min; (b) within 1.5 h; (c) within 2.5 h. The numbers in spectra (a) and (c) indicate the positions of the dihydropyridine ring of **3a** and "free" BNAH, respectively. The peaks attributable to the methylene protons of the benzyl groups are displayed by $-CH_2-$ and ($-CH_2-$). The proton at the 2-position of "free" BNAH was observed at 6.94 ppm, which is not illustrated in this figure.

The rhenium hydrido complex $[Re(bpy)(CO)_3H]$ (**2**) also reacts with BNA^+ to give the 1:1 adduct **3b** (Scheme 1).[6,7] Similar adduct formation occurred for the reactions of **1** with the acetyl analogue ($BAcP^+$) and the diethylcarbamoyl derivative (BEt_2NA^+) to give **3c** and **3d**, respectively, in quantitative yield (Scheme 1).[6] All of the adducts were again quantitatively cleaved to the corresponding 1,4-dihydropyridine products and the solvento complexes. It is of significance to note that either **1** or **2** does form an adduct of similar structure, irrespective of their substantially different electrochemical and steric properties.[8] The adduct formation described in this paper is the first identified example to our knowledge but might be a

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(6) It has been reported that ν_{CO} of formamide is shifted down to 41 cm^{-1} lower frequency compared to "free" formamide by coordination to a cobalt(II) complex. See: Balahura, R. J.; Jordan, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 1533. The carbonyl stretching frequencies (ν_{CO}/cm^{-1}) of the substituents (X) at the 3-position of **3b**−**d** measured in CD_3CN and their differences ($\Delta\nu_{CO}$/cm^{-1}) from those of the corresponding "free" NAD(P)H models (written in parentheses) are 1519 (−60), 1519 (−64), and 1550 (−54), respectively.

(7) There are two possible isomers of **3a** and **3b**, i.e., N-bonded (M−$NH_2C(O)R$) and O-bonded (M−$OC(NH_2)R$) isomers. Unfortunately, all the spectral data obtained in this study do not give us clear evidence for determining the bond form of the adducts. An X-ray crystallographic study is in progress.

(8) The oxidation potentials of **1** and **2** were 0.17 and 0.9 V vs SCE in acetonitrile, respectively. See: Konno, H.; Kobayashi, A.; Sakamoto, K.; Fagalde, F.; Katz, N. E.; Saitoh, H.; Ishitani, O. *Inorg. Chim. Acta* **2000**, *299*, 155; Sullivan, B. P.; Meyer, T. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1244.

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common key pathway working in the regioselective NAD(P) reduction promoted by the transition-metal complexes.[3,5]

To obtain mechanistic insights into the reactions, we carried out kinetic studies on the adduct formation between BNA^+ and the metal hydrido complexes using stopped-flow and rapid-scan methods. Since the observed pseudo-first-order rate constants linearly increased with the concentration of BNA^+ up to 300 times higher than for the hydrido complexes, the reactions between the metal hydrido complexes and BNA^+ should follow a second-order kinetic law. The second-order rate constants for the reactions of BNA^+ with **1** and **2** in DMF were determined to be 1.7×10^3 and 9.6×10^2 M^{-1} s^{-1} at 27 °C, respectively. The rate constants revealed temperature dependence, from which linear Arrhenius plots were obtained between 12 and 57 °C to give the following thermodynamic data for the adduct formation: $\Delta S^{\ddagger} = -149$ J mol^{-1} and $\Delta H^{\ddagger} = 10$ kJ mol^{-1} for **3a**, and $\Delta S^{\ddagger} = -51$ J mol^{-1} and $\Delta H^{\ddagger} = 42$ kJ mol^{-1} for **3b**.

On the basis of the above observations, a possible mechanistic pathway for the adduct formation can be envisaged as follows. Either the carbamoyl or acetyl group of the NAD(P) models should preferentially undergo nucleophilic interactions with the Ru^{II} and Re^{I} centers of the hydrido complexes to give the corresponding activated complexes, the hydrido ligand of which might also nucleophilically interact with the pyridinium moiety. The observed large negative activation entropies for the adduct formation imply that conformations of the activated complexes should be tightly fixed to favor the specific transfer of the hydride ligand to the 4-position of the NAD(P) models to occur. On the other hand, steric hindrance due to the benzyl substituent is probably too high to allow a conformational change favorable for hydride transfer to the 2-position. Another possible site for hydride transfer would be the 6-position, but this position is too far from the metal center interacting with the carbamoyl or acetyl group.

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Supporting Information Available: Tables, figures, and text giving experimental details, ^1H NMR and ESI-MS data for **3a**−**d**, and kinetic data for formation of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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