to the integrated intensity with a SADABS program. The structure solution was performed on a SHELXTL software package. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-142966 and -142967. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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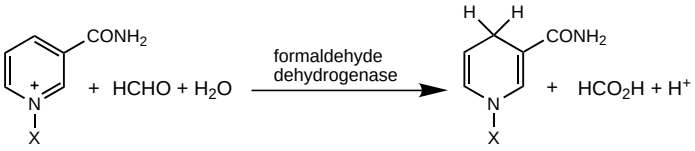
Regiospecific Hydride Transfer from *cis*-[Ru(bpy)$_2$(CO)(CHO)]$^+$ to NAD$^+$ Model Compounds: A Model for Enzymatic Reactions by Aldehyde Dehydrogenases**

Hideo Konno, Kazuhiko Sakamoto, and Osamu Ishitani*

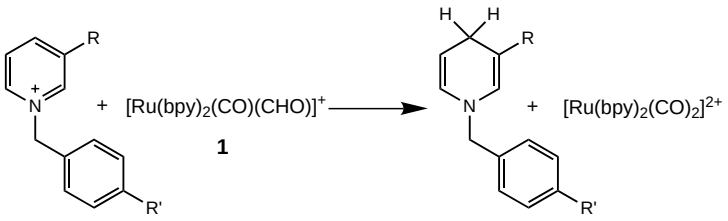
The nicotinamide adenine dinucleotide coenzyme NAD$^+$ is required for the clearance of potentially toxic aldehydes by the enzymes of the aldehyde dehydrogenase (ALDH) family.[1, 2] For example, the oxidation of formaldehyde by NAD$^+$ occurs in the presence of the formaldehyde dehydrogenase (EC 1.2.1.46.) to give formic acid and 1,4-NADH (Scheme 1).[3] A crucial point of this reaction is the direct and



Scheme 1. The oxidation of formaldehyde by NAD$^+$ in the presence of formaldehyde dehydrogenase. For clarity, only the pyridine ring of NAD$^+$ and the 1,4-dihydropyridine ring of NADH are shown; the remainder of the molecule in each case is represented by X.

regiospecific hydrogen transfer from the carbonyl carbon of the aldehyde to the 4-position of the pyridinium ring of NAD$^+$.[4] In nonbiological systems, however, only a few nonenzymatic models for this important biological reaction have been reported so far.[5] Herein we report the regiospecific reduction of NAD$^+$ model compounds **2a–e** by a ruthenium formyl complex *cis*-[Ru(bpy)$_2$(CO)(CHO)]PF$_6$ (**1**; bpy = 2,2′-bipyridine) which acts as a mimic of the formaldehyde dehydrogenase reaction.

In a typical run, the reaction of **1** (7.6 mmol) with **2a** (11.4 mmol) was carried out in CD_3CN (0.75 mL) at 0 °C under an argon atmosphere in dim light, and the progress of the reaction was monitored by ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectroscopy. Within a few minutes, 1-benzyl-1,4-dihydronicotinamide (**3a**) and an equimolecular amount of *cis*-[Ru(bpy)$_2$(CO)$_2$]$^{2+}$ were produced in a quantitative yield based on the quantity of **1** used in the reaction (Scheme 2). The other isomers of dihydronicotinamide, that is, the 1,2-dihydro and 1,6-dihydro forms, were not detected at all.



Scheme 2. The reduction of NAD$^+$ models **2a–e** by the ruthenium complex **1**. For respective R and R′ groups, see Table 1. For reaction conditions, see text.

Other NAD$^+$ models with various electron-withdrawing groups at the 3-position were also regioselectively reduced by **1** to give the corresponding 1,4-dihydro forms (Scheme 2). Table 1 contains a summary of the results of the reactions, together with the reduction potentials of **2a–e**. The reductions of **2a–d** were completed within 15 min along with the quantitative formation of the corresponding 1,4-dihydro forms. In the case of **2e**, the reaction was negligible at 0 °C but occurred significantly at 25 °C to result in selective formation of **3e**, albeit in lower yield than was obtained from the other NAD$^+$ models.

In order to identify the hydrogen origin for the selective reduction of **2a–e**, isotope experiments were carried out by two methods. The reduction of **2a** with *cis*-

[*] Prof. O. Ishitani, H. Konno, Prof. K. Sakamoto
Graduate School of Science and Engineering
Saitama University
255 Shimo-Okubo, Urawa, Saitama 338-8570 (Japan)
Fax: (+81) 48-858-3818
E-mail: ishitani@apc.saitama-u.ac.jp

[**] bpy = 2,2′-Bipyridine. We acknowledge helpful discussions with Dr. Chyongjin Pac (Kawamura Institute of Chemical Research). We also thank the Kojima Chemical Company for a generous gift of pure $RuCl_3 \cdot 3H_2O$.

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Table 1. Results of the reduction of NAD^+ model compounds **2a–e** by *cis*-$[Ru(bpy)_2(CO)(CHO)]PF_6$ (**1**; see Scheme 2) and the reduction potentials E_{cp} of the models.[a]

NAD^+ models	R	R′	*t* [min]	Conversion of **1** [%]	Yield of **3** [%][b]	E_{cp} [V][c]
2a	$CONH_2$	H	15	100	100	−1.36
2b	CF_3	H	15	100	100	−1.23
2c	$COCH_3$	H	15	100	100	−1.26
2d	$CONH_2$	CH_3	15	100	100	−1.40
2e	$CONEt_2$	H	30	15	20	−1.43
2e	$CONEt_2$	H	300	100	20	−1.43

[a] The reactions of the NAD^+ model compounds **2a–2d** with **1** were carried out at 0 °C in a CD_3CN solution. With model compound **2e** the reaction was performed at 25 °C. [b] Based on the amount of **1** consumed during the reaction. [c] Reduction potentials were measures against Ag/Ag^+ and were irreversible. The scan rate was 200 mV s^{-1}.

$[Ru(bpy)_2(CO)(CDO)]^+$ (>95% D) resulted in almost quantitative deuterium incorporation (>95%) at the 4-position of **3a**. By contrast, no deuterium incorporation into the dihydropyridine ring of **3a** occurred in the reaction of **2a** with **1** in a CD_3CN solution containing a drop of D_2O, while the exchangeable protons of the carbamoyl group were quantitatively deuterated. This clearly demonstrates that regiospecific hydrogen transfer occurs from the formyl ligand to the 4-position of the pyridinium ring of **2a**. This is probably true for the reduction of the other NAD^+ models. Since the formyl ligand of **1** can be regarded as an activated form of formaldehyde coordinated to the Ru^{II} center, the present reactions of the NAD^+ model compounds with **1** might provide a useful mimic for the formaldehyde dehydrogenase reaction.[6] In this regard, it should be noted that "free" formaldehyde is essentially unreactive with NAD^+ models.[7]

Recently, Kanomata and co-workers reported that a magnesium 1,1-diolate compound can reduce some particular NAD^+ models with relatively high regioselectivities.[5] This might be considered as the first example of an aldehyde (D-glyceraldehyde-3-phosphate) dehydrogenase model. In this model, however, the regioselective reduction occurs only for particular NAD^+ models possessing a bulky tertiary amide group, while the reactions of conventional model compounds are accompanied by significant formation of other isomeric products, for example, the 1,6-dihydro form in 5–27% yield. This is in contrast to the present model reactions that have accomplished the efficient regiospecific reduction of the typical NAD^+ models, such as **2a**, into the 1,4-dihydro products, as shown in Table 1.

Among the reductants used for regioselective reductions of NAD^+ and model compounds in nonenzymatic systems,[8a] sodium dithionite has been most often used as a conventional reductant. In the reactions using this reductant, however, the other isomers of the 1,4-dihydro form are produced in significant quantities as by-products. This is probably, at least in part, due to thermal isomerization of the initially formed 1,4-dihydro form to the other isomers,[8] because the reactions of NAD^+ models with this reductant require high temperatures and relatively long reaction times. Metal hydrides are also interesting reductants for NAD^+ and models,[9] but some of them have serious limitations arising from the isomerization of the 1,4-dihydro form into other isomers, a process catalyzed by intermediates produced from the starting metal complexes,[9b,c] as well as from the remarkable dependence of the reduction capability on the structures of the NAD^+ derivatives.[9d] Compared with such reductants, **1** certainly has an advantage in the efficient regiospecific 1,4-reduction of a wide variety of NAD^+ models and, hence, the present system is potentially useful as a preparative method for various 1,4-NADH model compounds.

With regard to the regiospecificity in the present reactions, it is reasonable to assume that interactions of the Ru^{II} center[10] or the formyl carbon with the substituents at the 3-position of the NAD^+ models control the hydrogen transfer from **1** to the 4-position of **2a–e**, as suggested by Fish and coworkers for reductions of NAD^+ models using $[Cp^*Rh(bpy)H]^+$ (Cp^* = pentamethylcyclopentadienyl).[9b] This mechanistic assumption is apparently in accord with the much slower reactivity of **2e** which has the bulky diethyl carbamoyl group, since the steric congestion of the carbamoyl group should inhibit interactions of the carbamoyl oxygen and/or nitrogen with the Ru complex. Nevertheless, the reduction of **2e** is regiospecific, indicating the essential role of the Ru complex–carbamoyl interactions in the hydrogen transfer. The low yield of **3e** is due to the significant chemical changes in **1** which occur at the reaction temperature (25 °C) to give $[Ru(bpy)_2(CO)(CD_3CN)]^{2+}$, $[Ru(bpy)_2(CO)(CH_2OH)]^+$, and other unidentified compounds.[11] In the case of **2b**, the CF_3 group might interact with the Ru complex through the electronegative fluorine atoms. Such interactions would certainly be weaker than those of the carbamoyl and acetyl groups but would still be effective enough to control the regiochemistry in the hydrogen transfer. Studies into the mechanistic details and synthetic applications of the present reactions are in progress.

Experimental Section

Formyl complex **1** was prepared according to the reported procedure,[10a] and a similar method was used for the synthesis of $[Ru(bpy)_2(CO)(CDO)]^+$ using $NaBD_4$ (98 atom% D), MeOD (99.5 atom% D), and D_2O (99.8 atom% D); the deuterium purity of the product was confirmed to be >95% using ^1H NMR spectroscopy. The NAD^+ and NADH model compounds were synthesized according to reported procedures[8, 12] or by methods similar to that required for **2a**. The melting points, elemental analysis results, and ^1H NMR and ^{13}C NMR spectroscopic data of the new model compounds are as follows:

2b: m.p.: 118–119 °C (decomp); ^1H NMR (400 MHz, CD_3CN): $\delta = 9.20$ (s, 1H; H-2), 8.91 (d, $J = 6.2$ Hz, 1H; H-6), 8.80 (d, $J = 8.2$ Hz, 1H; H-4), 8.21 (dd, $J = 8.2$, 6.2 Hz, 1H; H-5), 7.49 (m, 5H; Ph), 5.78 (s, 2H; CH_2Ph); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 148.9$, 144.5, 143.9, 132.9, 131.3, 130.8, 130.6, 130.6, 66.3; elemental analysis: calcd for $C_{13}H_{11}F_9NP$ (383.20): C 40.75, H 2.89, N 3.66; found: C 40.47, H 2.76, N 3.67.

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2d: m.p.: 101 – 102 °C (decomp); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 9.12$ (s, 1H; H-2), 8.80 (d, $J = 6.2$ Hz, 1H; H-6), 8.75 (d, $J = 8.1$ Hz, 1H; H-4), 8.09 (dd, $J = 8.1$, 6.2 Hz, 1H; H-5), 7.35 (d, $J = 8.0$ Hz, 2H; Ph), 7.29 (d, $J = 8.0$ Hz, 2H; Ph), 7.13 (br. s, 1H; $CONH_2$), 6.57 (br. s, 1H; $CONH_2$), 5.70 (s, 2H; CH_2Ph), 2.35 (s, 3H; CH_3); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 163.7$, 146.9, 145.4, 145.0, 141.4, 135.5, 131.1, 130.5, 130.4, 129.5, 65.7, 21.3; elemental analysis: calcd for $C_{14}H_{15}F_6N_2OP$ (372.25): C 45.17, H 4.06, N 7.53; found: C 45.33, H 3.93, N 7.52.

Cyclic voltammograms of the NAD^+ model compounds were measured in acetonitrile solution that contained tetra-*n*-butylammonium tetrafluoroborate (0.1M) as the supporting electrolyte. An ALS/CHI CHI-620 electrochemical analyzer, with a Pt disk working electrode, an $Ag/AgNO_3$ (0.01M) reference electrode, and a Pt counter electrode was used for the analysis.

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A New Self-Assembling System for Targeted Gene Delivery**

Michael A. W. Eaton,* Terence S. Baker, Catherine F. Catterall, Kenneth Crook, Graham S. Macaulay, Barbara Mason, Timothy J. Norman, David Parker,* Justin J. B. Perry, Richard J. Taylor, Alison Turner, and A. Neil Weir

The goal of targeted nonviral gene therapy has aroused considerable interest amongst scientists in recent years.[1] The ability to deliver recombinant DNA both selectively and efficiently to a given cell-type requires several features working effectively in harmony. Preferably the DNA needs to be compacted to protect it from enzymatic attack,[2] and tightly bound to a suitable targeting ligand.[1b] The resultant vector needs to be efficiently delivered to the target cell population with sufficient selectivity to minimize unwanted interaction with other cell types. Finally, once internalized into the desired cell the DNA must escape from the endosome into the cytoplasm[3] and enter the nucleus while being protected from the action of nucleases en route. Each of the above stages presents a major scientific challenge and different strategies have been formulated. Cationic liposomes, for example, have been studied in detail,[4] but lack specificity in targeting and generally yield heterogenous complexes with DNA. Cationic polymers, notwithstanding their toxicity in vivo, strongly bind DNA and may afford a pH-dependent release mechanism through a conformational change in the polymer in the more acidic medium of an endosome.[5] We now report our preliminary work to develop a new modular supramolecular approach to overcome the challenges associated with targeted gene delivery.

Compaction of DNA in nature is achieved through charge neutralization of the polyanion by interaction with the protonated polyamine spermine.[6] Accordingly, we have prepared a series of amphiphilic tetra- and hexaamines **1** – **12**, which as a consequence of the C_3 or C_4 spacing between each nitrogen site possess 3.6 or 5.2 positive charges at

[*] Dr. M. A. W. Eaton,[+] T. S. Baker, Dr. C. F. Catterall, Dr. K. Crook, Dr. G. S. Macaulay, B. Mason, Dr. T. J. Norman, Dr. R. J. Taylor, A. Turner, Dr. A. N. Weir
Celltech Chiroscience Ltd.
216 Bath Road, Slough, SL1 4EN (UK)
Fax: (+44) 1753-536-632
E-mail: meaton@celltech.co.uk
Prof. D. Parker, Dr. T. J. Norman, Dr. J. J. B. Perry
Department of Chemistry
University of Durham
South Road, Durham, DH1 3LE (UK)
Fax: (+44) 191-386-1127
E-mail: david.parker@dur.ac.uk

[+] Present address:
Swords Laboratories, Bristol Myers Squibb
Watery Lane, Swords, Co. Dublin (Ireland)

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