CHEMISTRY LETTERS, pp. 1599-1602, 1989.

Reductive Methylation of NAD^+ Analogues by a trans-Dimethylcobalt(III) Complex

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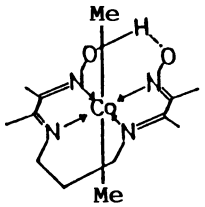
Various NAD^+ analogues are readily reduced by a trans-dimethylcobalt(III) complex to yield the corresponding methylated NADH analogues, while cis-dialkyl- or monoalkylcobalt(III) complexes cannot reduce the NAD^+ analogues at all.

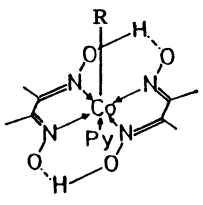
Nicotinamide adenine dinucleotide (NAD^+) is reduced by fuel molecules in the citric acid cycle to yield the corresponding 1,4-dihydronicotinamide (NADH), which is provided for respiratory chain. Thus, there has been considerable interest in reduction of pyridinium ions used as NAD^+ analogues to the corresponding dihydropyridines.[1-3] Reduction of pyridinium ions by organometallic reagents to yield substituted dihydropyridines has also been extensively studied, since the substituted dihydropyridines are valuable synthetic intermediates for a variety of alkaloids as well as NADH analogues.[4] With respect to the alkylating reagents, however, they have so far been limited to strong reductants, such as alkyllithium,[4] alkyl-Grignard,[4,5] alkylzinc,[6] and alkylcopper[7] reagents.

On the other hand, the vitamin B_{12} coenzyme and related alkylcobalamins are known as unique naturally occurring organometallic reagents of great biological significance.[8] However, there has so far been no report on the reduction of NAD^+ analogues by alkylcobalt(III) complexes which are known as rather mild reducing reagents.[9] In this study, we report that various NAD^+ analogues can be reduced readily by a trans-dialkylcobalt(III) complex, trans-$[Me_2Co(DpnH)]$ (DpnH 11-hydroxy-2,3,9,10-tetramethyl-1,4,8,11-tetraazaundeca-1,3,8,10-tetraene-1-olate).

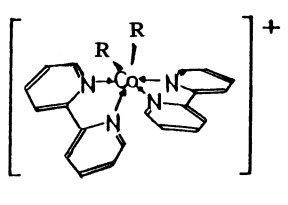
Alkylcobaloximes, $[RCo(DH)_2py]$ (R = Me and Et; $(DH)_2$ = bis(dimethylglyoximato); py = pyridine), frequently used as coenzyme B_{12} analogues,[10] showed no reactivity towards 10-methylacridinium ion ($AcrH^+$) which is known as a relatively strong oxidant among various NAD^+ analogues.[11] Dialkylcobalt(III) complexes, cis-$[R_2Co(bpy)_2]ClO_4$ (R = Me and Et; bpy = 2,2'-bipyridine), which are stronger reductants than $[RCo(DH)_2py]$,[12] did not react with $AcrH^+$ in acetonitrile, either.



trans-$[Me_2Co(DpnH)]$



$[RCo(DH)_2py]$



cis-$[R_2Co(bpy)_2]^+$

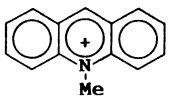
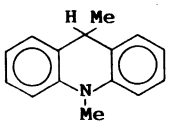
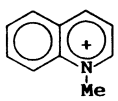
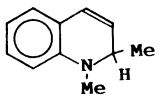
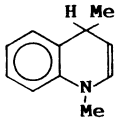
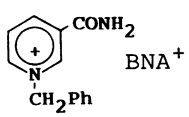
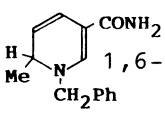
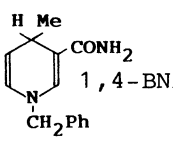
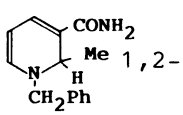
When a sterically less hindered dialkylcobalt(III) complex as compared with cis-dialkylcobalt(III) complexes, trans-[$Me_2Co(DpnH)$],[13] is used as a reductant, however, $AcrH^+$ is reduced readily by trans-[$Me_2Co(DpnH)$] to yield 9,10-dimethylacridine (AcrHMe) selectively (Eq. 1). The formation of $[MeCo(DpnH)]^+$ was

$$\text{trans-}[Me_2Co(DpnH)] + AcrH^+ \longrightarrow [MeCo(DpnH)]^+ + AcrHMe \quad (1)$$

confirmed by the ^1H NMR spectrum.[12] The trans-[$Me_2Co(DpnH)$] complex can reduce other NAD^+ analogues, 1-methylquinolinium ions ($X\text{-}QuH^+$; X= 3-CN, 3-Br, H, and 2-Me) and 1-(X-benzyl)nicotinamidium ion ($X\text{-}BNA^+$; X = 4-NO_2, 2,4-Cl_2, 4-Cl, H, and 4-MeO), to yield the corresponding methylated NADH analogues (methylated 1,2- and 1,4-dihydroquinolines and -dihydronicotinamides). The relative amounts of the isomers present in the initial product mixtures were determined from the ^1H NMR (400 MHz) spectra under the conditions that the amount of a reductant is slightly excess to that of the NAD^+ analogue in order to avoid the possible isomerization in the presence of the unreacted NAD^+ analogue, as reported in the literature.[14] The typical product distributions are shown in Table 1. For the reduction of $X\text{-}QuH^+$, the 1,2-isomers predominate and no or little amount of the 1,4-isomer is formed (Table 1). In the case of BNA^+, the 1,6-isomer predominates, but a comparable amount of the 1,4-isomer is formed together with a small amount of the 1,2-isomer.

Rates of the reduction of various NAD^+ model compounds by trans-[$Me_2Co(DpnH)$] were followed by the decay of the absorption band due to trans-[$Me_2Co(DpnH)$] (λ_{max} 407 nm). The rates obeyed the second-order kinetics, showing the first-order dependence on the concentration of each reactant. The observed second-order rate

Table 1. Reduction of NAD^+ Analogues (4.0×10^{-2} mol dm^{-3}) by trans-[$Me_2Co(DpnH)$] (4.1×10^{-2} mol dm^{-3}) in Acetonitrile at 298 K

NAD^+ analogue	Product (yield / %)[a]	
 $AcrH^+$	 AcrHMe (100)	
 QuH^+	 1,2-QuHMe (100)	 1,4-QuHMe (trace)
3-$CNQuH^+$	3-CN-1,2-QuHMe (78)	3-CN-1,4-QuHMe (22)
3-$BrQuH^+$	3-Br-1,2-QuHMe (91)	3-Br-1,4-QuHMe (9)
2-$MeQuH^+$	2-Me-1,2-QuMe (100)	2-Me-1,4-QuHMe (trace)
 BNA^+	 1,6-BNAMe (51)	 1,4-BNAMe (37)  1,2-BNAMe (12)

a) Determined using a 400 MHz JEOL JNM-GSX-400 NMR spectrometer.

Table 2. Observed Second-Order Rate Constants k_{obsd} of the Reduction of NAD^+ Analogues by trans-[Me_2Co(DpnH)] in Acetonitrile at 298 K, the One-Electron Reduction Potentials (E^0_{red} vs. SCE) of NAD^+ Analogues, and the Calculated Rate Constants k_{et} of Outer-Sphere Electron Transfer from trans-[Me_2Co(DpnH)] to NAD^+ Analogues

NAD^+ analogue	E^0_{red} [a]	k_{obsd}	k_{et} [b]
	V	$dm^3\ mol^{-1}\ s^{-1}$	$dm^3\ mol^{-1}\ s^{-1}$
$AcrH^+$	-0.43[c]	4.1	6×10^{-6}
3-$CNQuH^+$	-0.60	7.3×10	8×10^{-9}
3-$BrQuH^+$	-0.76	1.2×10	2×10^{-11}
QuH^+	-0.96	2.8×10^{-2}	7×10^{-15}
2-$MeQuH^+$	-1.05	3.5×10^{-4}	2×10^{-16}
4-NO_2BNA^+	-0.98	3.6×10^{-2}	3×10^{-15}
2,4-Cl_2BNA^+	-1.08[c]	1.8×10^{-2}	6×10^{-17}
4-$ClBNA^+$	-1.08[c]	6.8×10^{-3}	6×10^{-17}
BNA^+	-1.08[c]	2.6×10^{-3}	6×10^{-17}
4-$MeOBNA^+$	-1.13	3.8×10^{-3}	9×10^{-17}

a) Determined by the analysis of the cyclic voltammogram.[1,11] b) Calculated as the maximum value for the outer-sphere electron transfer. c) Ref. 11.

constants k_{obsd} of various NAD^+ analogues are listed in Table 2, together with the one-electron reduction potentials E^0_{red}, which were determined by the analysis of the cyclic voltammograms as described elsewhere.[1,11] The k_{obsd} value increases with the positive shift in the E^0_{red} value as the electron transfer from trans-[Me_2-Co(DpnH)] to NAD^+ analogues becomes energetically more favorable. In order to evaluate the contribution of such an electron transfer process, the rate constants k_{et} of the electron transfer are calculated by Eq. 2, where Z is the collision

$$k_{et} = Z\exp[-F(E^0_{ox} - E^0_{red})/RT] \quad (2)$$

frequency, taken as 1×10^{11} $dm^3\ mol^{-1}\ s^{-1}$,[15] F is the Faraday constant, and E^0_{ox} is the one-electron oxidation potential of trans-[Me_2Co(DpnH)].[16] As shown in Table 2, the k_{obsd} values are 10^6 – 10^{14}-fold larger than the k_{et} values which are considered as the maximum values for the outer-sphere electron transfer.[15] Such large discrepancies between the k_{obsd} and k_{et} values may exclude an outer-sphere electron pathway, and thus the reduction of NAD^+ analogues by trans-[Me_2Co(DpnH)] may proceed via a direct carbanion transfer. The carbanion (Me^-) may attack predominantly the C-2 position of X-QuH^+ and the C-6 position of X-BNA^+ to yield X-1,2-QuHMe and X-1,6-BNAMe as the main products, respectively (Table 1), since essentially the same regioselectivities have been reported for the hydride reduction of the NAD^+ analogues by $NaBH_4$.[14]

Alternatively, an inner-sphere electron transfer may occur following the formation of an inner-sphere complex in which a strong interaction between the cobalt-carbon bond and the NAD^+ analogue may exist. Upon the electron transfer, the methyl ligand is transferred to the NAD^+ analogue via the facile cleavage of

the cobalt-carbon bond of trans-$[Me_2Co^{IV}(DpnH)]^+$, followed by the coupling of the methyl radical with the corresponding NAD· analogue to yield the methylated NADH analogues. The dependence of k_{obsd} on E^0_{red} (Table 2) may be ascribed to the contribution of such an inner-sphere electron-transfer pathway. At present, however, it is difficult to distinguish between the two pathways; a direct carbanion transfer and an inner-sphere electron transfer. In any case, a strong interaction between the cobalt-carbon bond and NAD^+ analogues may be essential for the reaction to occur, since no reduction of NAD^+ model compounds occurs by sterically more hindered complexes, cis-$[R_2Co(bpy)_2]^+$, despite of the similar E^0_{ox} values (0.63 and 0.57 V vs. SCE for R = Me and Et, respectively)[12] compared with that of trans-$[Me_2Co(DpnH)]$ (0.53 V vs. SCE).[16]

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(Received June 26, 1989)