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Reduced Nicotinamide Adenine Dinucleotide (NADH) Models. 14.[1] Metal Ion Catalysis of the Reduction of α,β-Unsaturated Ketones by 1,4-Dihydropyridines. A Model of Δ^4-3-Ketosteroid Reductases

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Abstract: The reduction of (*E*)-2-, (*E*)-3- and (*E*)-4-cinnamoylpyridines by 1,4-dihydropyridine derivatives, to the corresponding dihydro ketones, is catalyzed by Zn^{2+} and Mg^{2+} ions. Kinetic measurements show that the rate of reduction is fastest in the case of the 2 isomer, in which the metal ion is simultaneously complexed with the nitrogen and the oxygen sites. The latter example is regarded as a model of electrophilic catalysis of the NADH-dependent enzymatic reduction of Δ^4-3-ketosteroids. Reduction of the above-mentioned substrates, as well as that of the (corresponding) isomeric β-benzoylvinylpyridines, with 1,4-dihydropyridine-*4,4-d*$_2$ reveals that in all reduction products the deuterium atom is located at the β position with respect to the carbonyl group. Furthermore, in the reaction of (*E*)-2-cinnamoylpyridine with *N*-benzyl-1,4-dihydronicotinamide-*4,4-d*$_2$ the primary kinetic isotope effect shows that C(4)–H bond cleavage is involved in the rate-determining step. These results are interpreted in terms of a mechanism involving either a hydride transfer or a sequential transfer of an electron (e) and a hydrogen atom (H·).

A number of pyridine nucleotide linked dehydrogenases catalyze the redox equilibrium >C=C< ⇌ >CH—CH<, involving the double bond function of α,β-unsaturated ketones.[3] Although several examples of the reduction of electrophilic olefins by NAD(P)H models have been reported in the literature,[4] the systems studied thus far correspond to "internally activated" substrates rather than models in which the activation of the substrate is derived from catalytic features corresponding to those present in the enzyme. For a variety of pyridine nucleotide dependent dehydrogenases, an electrophilic catalysis of the reduction step (mediated by coordinated or covalently bound electrophiles) has been postulated.[5,6] Model reactions illustrating electrophilic catalysis of the reduction of α,β-unsaturated ketones may be visualized in terms of the reduction of the double bond in systems corresponding to A or B (Figure 1) by suitable 1,4-dihydropyridines. In A, an electrophilic catalyst is subtended toward the carbonyl oxygen by virtue of its coordination to a suitable site on the protein matrix. In B, on the other hand, the same electrophile is attached to the apoenzyme via a covalent bond. In the current phase of our work on the reduction of conjugated enones, attention has been directed to model system A. At a molecular level a system such as A is subject to extensive variation.

We have chosen the pyridyl ketones **3a–c** as model substrates, since they allow the investigation of electrophilic catalysis of the reduction step, according to the mechanism implied in A. Metal ions that are known to coordinate to the pyridine nitrogen could potentially act as electrophilic centers. In the case of 2-cinnamoylpyridine (**3a**), it is anticipated that a metal cation would directly coordinate with both the nitrogen of the pyridine ring and the oxygen of the carbonyl group. Since exclusive nitrogen coordination in **3a** also activates the α,β-unsaturated carbonyl function via electron withdrawal, catalysis due to direct interaction between the electrophile and the C=O group should be revealed by comparison of reduction rates of the 2- and 4-cinnamoylpyridines (**3a** and **3c**). In this article we present evidence for bidentate coordination of **3a** with magnesium and zinc ions and show that such coordination leads to catalysis of reduction of **3a** by 1,4-dihydropyridine derivatives (NADH models).

Experimental Section

Methods. UV spectra were determined using a Cary Model 14 recording spectrophotometer with acetonitrile as solvent. Infrared spectra as well as far-infrared spectra of enones **3a–c**, **4a–d**, **3a**·$HClO_4$, **4a**·$HClO_4$ and the complexes **9a** and **9b** were taken on a Beckman IR-4250 spectrophotometer using KBr pellets (IR) or Nujol mulls (far-IR). IR spectra of other compounds were taken on a Perkin-Elmer 125 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian HA-100 or XL-100-12 instrument. Chemical shifts are reported in units of δ, downfield from internal tetramethylsilane, except for the spectra in CD_3CN, where δ_{CD_3CN} = 1.94 ppm was employed as an internal standard. ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer. Chemical shifts are reported in parts per million from internal Me_4Si. Coupling constants are given in hertz. Elemental analyses have been performed by H. Pieters of this laboratory.

Materials. Acetonitrile was dried by successive distillation over P_4O_{10} and K_2CO_3 and distilled again, before storage.[7] Prior to use the stored solvent was freshly distilled. $Mg(ClO_4)_2$ and $Zn(ClO_4)_2$ were employed as their hexaethanolates,[8] $M^{2+}(C_2H_5OH)_6(ClO_4^-)_2$ (M^{2+} = Mg^{2+} or Zn^{2+}).

1-Benzyl-1,4-dihydronicotinamide (BNAH, **2**)[9] and **3,5-diethoxycarbonyl 2,6-dimethyl-1,4-dihydropyridine** (HE, **1**)[10] were prepared according to literature procedures. **1-(2-Pyridyl)-3-phenylprop-2-en-1-one** (2-CP, **3a**) was synthesized according to the method of Annigeri and Siddapa[11] and recrystallized from ethanol. For the synthesis of **3-(2-pyridyl)-1-phenylprop-2-en-1-one** (2-iCP, **4a**), the procedure of Marvel et al.[12] was modified according to the method described by Hünig et al.[13] The product was recrystallized from ether/*n*-hexane, 1:5 (v/v), and obtained in 55% yield.

1-(3-Pyridyl)-3-phenylprop-2-en-1-one (**3b**), **1-(4-pyridyl)-3-phenylprop-2-en-1-one** (**3c**), **3-(3-pyridyl)-1-phenylprop-2-en-1-one** (**4b**), and **3-(4-pyridyl)-1-phenylprop-2-en-1-one** (**4c**) (3-CP, 4-CP, 3-iCP,

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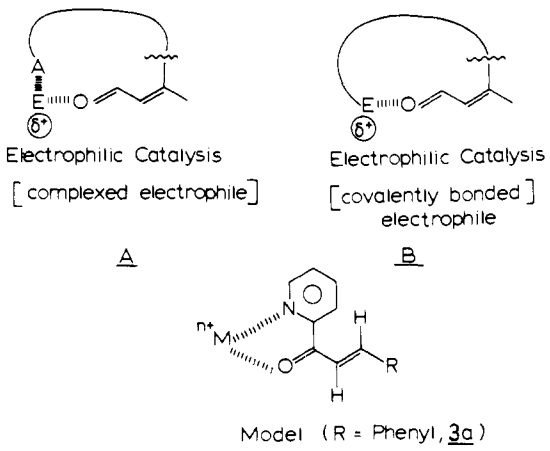


Figure 1. Models for electrophilic catalysis of the reduction of α,β-unsaturated ketones via complexation of the carbonyl oxygen.

and 4-iCP, respectively) were synthesized according to the method of Bieganowska.[14] ^{13}C NMR spectral data of **3a–c** and **4a–c** are presented in Tables I and II.

(*Z*)-3-(2-Pyridyl)-1-phenylprop-2-en-1-one (4d) was obtained by irradiation of a 2×10^{-2} M solution of the *E* isomer in acetonitrile with λ 366 nm and subsequent recrystallization of the resulting mixture (90% *Z* isomer and 10% *E* isomer; ^1H NMR) from *n*-heptane to give pure *Z* isomer as a white crystalline compound in 75% overall yield:[15] IR (KBr) $\nu_{C=O}$ 1659 cm^{-1}; $\nu_{C=C}$ 1581 cm^{-1}; far IR (Nujol mull) 402 (s), 392 (sh), 298 (vs), 237 (s), 208 (s), ^1H NMR (CD_3CN) δ H-3 7.57 (m, 1 H), H-4 7.81 (m, 1 H), H-5 7.33 (m, 1 H), H-6 8.68 (m, 1 H), H-α 7.73 and H-β 8.11 (AB system, J_{AB} = 12 Hz, 2 H), H ortho 8.08 (m, 2 H), H meta and H para ±7.65 (m, 3 H).

Reference samples for the reduction products of 2-CP and 2-iCP were obtained as follows: a 5×10^{-2} M solution of the enone 2-CP (**3a**) or 2-iCP (**4a**) in absolute ethanol was hydrogenated at room temperature at 2–3 atm over a catalytic amount of palladium on $CaCO_3$ in a Parr apparatus. The solution was filtered through Celite and concentrated. Using short reaction times (less than 30 min) the resulting colorless residue consisted of the corresponding saturated ketone, **5a** or **6a**, respectively. Longer reaction times (over 3 *h*) resulted in the corresponding saturated alcohols **7a** or **8a** as the sole product. Spectral data of the products were in agreement with those described in the literature.[19-23]

1-(2-Pyridyl)-3-phenylpropan-1-one (5a): IR ($CHCl_3$) $\nu_{C=O}$ 1700 cm^{-1}; ^1H NMR (CD_3CN) δ H-3 8.00 (m), H-4 7.89 (m), H-6 8.67 (m), 2H-α 3.54 (t), 2H-β 3.03 (t).

3-(2-Pyridyl)-1-phenylpropan-1-one (6a): IR ($CHCl_3$) $\nu_{C=O}$ 1680 cm^{-1}; ^1H NMR (CD_3CN) δ H-3 7.27 (m), H-4 7.65 (m), H-5 7.14 (m), H-6 8.48 (m), 2H-α 3.50 (t), 2H-β 3.20 (t).

1-(2-Pyridyl)-3-phenylpropan-1-ol (7a): IR ($CHCl_3$) ν_{OH} ±3400 (br); ^1H NMR (CD_3CN) δ H-6 8.59 (m), C(H)OH 4.75 (m), 2H-α ±2.05 (m), 2H-β 2.74 (m).

3-(2-Pyridyl)-1-phenylpropan-1-ol (8a): IR ($CHCl_3$) ν_{OH} ±3300 (br); ^1H NMR (CD_3CN) δ H-6 8.47 (m), C(H)OH 4.75 (m), 2H-α 2.19 (m), 2H-β 2.90 (m).

1-(2-Pyridyl)-3-phenylprop-2-en-1-ol (10a). To a suspension of 50 mg (1.35 mmol) of $LiAlH_4$ in 15 mL of dry ether, at 0 °C, was added a solution of 419 mg (2.0 mmol) of enone **3a** (2CP) in 10 mL of dry ether. The solution was stirred for 18 h and 1 mL of water, 0.1 mL of 15% aqueous sodium hydroxide, and 0.3 mL of water were added successively. The mixture was filtered, dried overnight (Na_2SO_4), and concentrated to give quantitatively the analytically pure alcohol, **10a**, as a colorless oil. The same results could be obtained by employing $NaBH_4$ in methanol as reducing agent. With $LiAlD_4$ or $NaBD_4$ as reducing agents, the monodeuterated allylic alcohol (**10a-*l*-d_1**) was obtained. This monodeuterated alcohol could be isomerized quantitatively to the corresponding saturated ketone **5a** as follows: 423 mg (2.0 mmol) of **10a** dissolved in 80 mL of ethanol/water, **4**:1 (v/v), was refluxed for 5 h in the presence of 5 g of K_2CO_3. The mixture was neutralized with 30% HCl and extracted with $CHCl_3$, and the combined extracts were washed with $NaHCO_3$, dried overnight (Na_2SO_4), and concentrated. The residue was recrystallized from *n*-heptane to afford 319 mg (75%) of (nondeuterated) **5a**: IR ($CHCl_3$) ν_{OH} 3380 (br), $\nu_{C=C}$ 1590 cm^{-1}; ^1H NMR (CD_3CN) δ H-6 8.57 (m), C(H)OH 5.40 (m), H-α 6.40 (m), H-β 6.85 (m), OH 2.55 (br). The $HClO_4$ salts of **3a** and **4a** could be prepared quantitatively by adding (dropwise) perchloric acid (70%, 1:1 in ethanol) to a 0.2 *m* solution of the appropriate enone in ether until just acid to Congo red. The solid obtained was filtered, washed with ethanol and ether, and dried.

1-(2-Pyridyl)-3-phenylprop-2-en-1-one hydroperchlorate (3a·$HClO_4$): IR (KBr) $\nu_{C=O}$ 1669 cm^{-1}, $\nu_{C=C}$ 1579 cm^{-1}; far-IR (Nujol mull) (450–200 cm^{-1}) 427 (m), 391 (w), 312 (vs), 282 (w); ^1H NMR (CD_3CN) δ H-3 8.88 (m), H-4 8.32 (m), H-5 7.85 (m), H-6 8.94 (m), H-α 8.26 (d) and H-β 7.74 (d), AB system J_{AB} = 16 Hz, H-2′ 7.83 (m, 2 H), H-3′, H-4′ 7.61 (m); ^{13}C NMR (CD_3CN + 1% Me_2SO-d_6) δ C-2 146.1, C-3 127.4, C-4 147.6, C-5 130.9, C-6 145.2; C(=O) 183.2, C-α 120.0, C-β 149.3, C-1′ 134.7, C-2′ 130.0, C-3′ 130.2, C-4′ 132.7.

3-(2-Pyridyl)-1-phenylprop-2-en-1-one hydroperchlorate (4a·$HClO_4$): IR (KBr) $\nu_{C=O}$ 1670 cm^{-1}; $\nu_{C=C}$ 1610 cm^{-1}; far-IR (Nujol mull) (450–200 cm^{-1}) 430 (m), 399 (w), 389 (m), 310 (vs), 268 (m), 228 (s); ^1H NMR (CD_3CN) δ H-3 8.43 (m), H-4 8.66 (m), H-5 8.04 (m), H-6 8.77 (m), H-α 7.71, and H-β 8.17, AB system J_{AB} = 16 Hz, H-2′ 8.11 (m, 2 H), H-3′ and H-4′ ±7.60 (m, 3 H); ^{13}C NMR (CD_3CN + 1% Me_2SO-d_6) δ C-2 148.5, C-3 127.0, C-4 147.1, C-5 133.1, C-6 143.1, C(=O) 189.0, C-α 127.9, C-β 132.8, C-1′ 137.3, C-2′ 129.5, C-3′ 129.6, C-4′ 134.7.

Dichlorobis[1-(2-pyridyl)-3-phenylprop-2-en-1-one]zinc(II) (9a). To a warm solution of 2 mmol of anhydrous $ZnCl_2$ in 5 mL of anhydrous ethanol was added, under magnetic stirring, a warm solution of 1 mmol of 1-(2-pyridyl)-3-phenylprop-2-en-1-one in 5 mL of anhydrous ethanol. Immediately, a yellowish green precipitate was formed. The mixture was maintained at 60 °C, with continuous stirring, for 5 min. After we allowed the mixture to cool to room temperature, the solid was filtered, washed with anhydrous ethanol, and dried in a desiccator over P_4O_{10}. The complex was recrystallized from anhydrous ethanol to afford **9a** in 50% yield: IR (KBr) $\nu_{C=O}$ 1650 cm^{-1} (vs), $\nu_{C=C}$ 1595 (vs); far-IR (Nujol mull) (450–200 cm^{-1})

Table I. ^{13}C NMR Chemical Shifts and $^1J_{CH}$ (in Parentheses) for 2-CP, 3-CP, 4-CP, and Chalcone in CD_3CN

position	compound			
	2-CP	3-CP	4-CP	chalcone
C-2	154.6	150.4 (180.3)	151.4 (180.0)	
C-3	123.1 (163.8)	133.9	122.2 (165.4)	
C-4	137.9 (166.2)	136.4 (164.3)	144.3	
C-5	127.9 (165.9)	124.4 (*)	122.2 (165.4)	
C-6	149.7 (180.1)	153.8 (179.9)	151.4 (180.0)	
C=O	189.6	189.5	190.1	190.4
C-α	121.7 (160.1)	122.6 (160.0)	122.3 (160.6)	123.0 (*)
C-β	144.4 (158.2)	145.5 (157.6)	146.5 (157.6)	144.7 (157.5)
C-1′	135.7	135.4	135.2	135.7
C-2′	129.3 (*)[a]	129.4 (*)	129.5 (*)	129.4 (*)
C-3′	129.7 (*)	129.7 (*)	129.7 (*)	129.7 (*)
C-4′	131.3 (161.8)	131.5 (161.9)	131.6 (161.9)	131.2 (161.3)

[a] *, not determined.

Table II. ^{13}C NMR Chemical Shifts and $^1J_{CH}$ (in Parentheses) for 2-iCP, 3-iCP, 4-iCP, and Chalcone in CD_3CN

position	compound			
	2-iCP	3-iCP	4-iCP	chalcone
C-2	153.8	150.8 (117.3)	151.1 (178.2)	
C-3	125.6 (165.6)	131.4	122.9 (*)	
C-4	137.6 (165.0)	135.3 (160.0)	142.7	
C-5	125.2 (166.0)	124.5 (166.3)	122.9 (*)	
C-6	150.8 (178.8)	151.6 (180.0)	151.1 (178.2)	
C=O	190.6	189.9	190.0	190.4
C-α	126.1 (161.9)	124.7 (160.0)	126.9 (160.5)	123.0 (*)
C-β	143.5 (159.2)	141.1 (158.9)	141.6 (160.5)	144.7 (157.5)
C-1′	138.5	138.5	138.2	138.8
C-2′	129.1 (*)[a]	129.2 (*)	129.3 (*)	129.2 (*)
C-3′	129.4 (*)	129.4 (*)	129.4 (*)	129.3 (*)
C-4′	133.7 (161.9)	133.7 (161.9)	133.9 (161.5)	133.4 (161.5)

[a] * not determined.

Table III. IR (KBr) Spectral Data of 2-Cinnamoylpyridine (**3a**) and Derivatives

	3a	9a	9b	3a·$HClO_4$
$\nu_{C=O}$	1672	1650 (−22)	1640 (−32)	1669 (−3)
$\nu_{C_\alpha=C_\beta}$	1606	1595 (−11)	1548 (−58)	1579 (−27)
$\nu_{C=N}$	1582	1604 (+22)	1604 (+22)	1614 (+32)
ν_{Zn-N}		245 (vs)	sym 264 (m) asym 286 (vs)	
ν_{Zn-O}		129 (s)	sym 152 (s) asym 168 (s)	
ν_{Zn-Cl}		282 (w)		
$\nu_{C_2-C(=O)}$ torsional vibration	311 (vs)	352 (m)	380 (m)	310 (s)

Table IV. Displacement of ^{13}C Chemical Shifts ($\Delta\delta$) upon Addition of $Mf(ClO_4)_2 \cdot 6C_2H_5OH$ to **3a–c** and **4a–c** and $Zn(ClO_4)_2 \cdot 6C_2H_5OH$ to **3a**

	3a	3b	3c	4a	4b	4c	3a + $Zn(ClO_4)_2$
C-2	−5.2	−1.0	−0.8	−0.3	−1.1	−1.2	−8.0
C-3	+5.2	+0.4	+1.0	−0.3	+0.8	+1.1	+5.5
C-4	+4.2	+1.8	+1.8	+0.6	+1.8	+2.0	+5.2
C-5	+3.1	+1.0	+1.0	+0.4	+0.9	+1.1	+4.0
C-6	+1.1	−1.0	−0.8	−0.3	−0.9	−1.2	+0.3
C(=O)	+2.6	−0.3	−0.1	+0.6	+0.3	+0.2	−0.2
C-α	−2.9	−0.5	−0.2	+0.3	+0.7	+1.3	−3.3
C-β	+9.5	+0.9	+0.9	0.0	−0.8	−0.9	+9.5

Table V. Biomolecular Rate Constants of the Reduction of **3a–c** and **4a–d** by 1-Benzyl-1,4-dihydronicotinamide (**2**) (CD_3CN, 23 °C; [Substrate] = [Reductant] = $[Mg^{2+}(ClO_4^-)_2]$ = 0.4 M)

substrate	reductant	k_2, M^{-1} min^{-1}	rel rate
3a	**2**	10.3	1590
3b	**2**	6.5×10^{-3}	1
3c	**2**	3.2×10^{-2}	5
3a	**2**-*4,4-d*$_2$	3.3	508
4a	**2**	3.7×10^{-3}	2.6
4b	**2**	1.4×10^{-3}	1
4c	**2**	4.3×10^{-3}	3.1
4d	**2**	5.0×10^{-3}	35.7

442 (w), 435 (m), 414 (m), 352 (m), 282 (w, Zn-Cl), 245 (vs, Zn-N), indicating a trans-planar octahedral structure. Anal. Calcd for ($C_{28}H_{22}Cl_2N_2O_2Zn$): C, 49.25; H, 3.25; Cl, 10.39; N, 4.10; Zn, 9.58. Found: C, 49.43; H, 3.36; Cl, 10.45; N, 4.20; Zn, 9.48.

Diperchloratobis[1-(2-pyridyl)-3-phenylprop-2-en-1-one]zinc(II) (9b). This complex was synthesized by the procedure described for **9a**, to give **9b** as a yellowish green powder in 75% yield: IR (KBr) $\nu_{C=O}$ 1640 cm^{-1} (s), $\nu_{C=C}$ 1548 cm^{-1} (vs); far-IR (Nujol mull) (450–140 cm^{-1}) 440 (m), 412 (m), 380 (s), 286 [vs, ν_{asym} (Zn-N)], 264 [m, ν_{sym} (Zn-N)], 168 [s, ν_{asym} (Zn-O)], 152 [s, ν_{sym} (Zn-O)] indicating a tetrahedral structure. Anal. Calcd for ($C_{28}H_{22}Cl_2N_2O_{10}Zn$): C, 60.62; H, 4.00; Cl, 12.78; N, 5.05; Zn, 11.79. Found: C, 60.70; H, 4.10; Cl, 12.65; N, 5.02; Zn, 11.86.

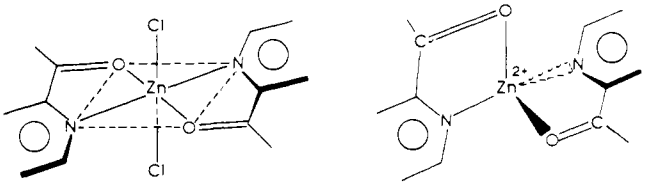
Complexation Studies. The interactions between metal ions and the unsaturated ketones **3a–c** and **4a–d** were investigated by observing the differences in spectral properties of the ketones upon addition of the metal salts. In the case of **3a**, the 2:1 complexes of the ketone with both $ZnCl_2$ and $Zn(ClO_4)_2$ have been synthesized.[24] By comparing the solid state (i.e., KBr) IR spectrum of the free ligand with the spectra of the aforementioned complexes, and from the far-IR spectral data (Nujol mull) (Table III), the structure of the complexes has been elucidated. The interaction of **3a–c** and **4a–d** with both $Mg(ClO_4)_2$ and $Zn(ClO_4)_2$, in acetonitrile, was observed by measuring the maximum chemical-shift differences in the ^{13}C NMR spectra of these ketones ([ligand] = 1.67 M in CD_3CN) upon addition of $Mg(ClO_4)_2$ or $Zn(ClO_4)_2$ (Table IV). The ^{13}C NMR data provide information on structures of the Mg(II) and Zn(II) complexes of **3a–c** and **4a–d** in acetonitrile solution.

Kinetic Studies. The kinetic measurements of the $Mg(ClO_4)_2 \cdot 6C_2H_5OH$-catalyzed reduction of **3a–c** and **4a–d** by **2** were carried out in anhydrous acetonitrile under a dry nitrogen atmosphere. The action rates were measured using ^1H NMR spectroscopy, in CD_3CN, under the conditions: [enone] = [reductant] = [metal salt] = 0.4 M, at 23 °C. The progress of the reaction was assayed (spectrometrically) by studying the decrease in intensity of the signals of the enone (H-6) and the reductant (H-4, H-5, H-6, CH_2), and by following the increase in intensity of the signals of the reduction product (H-6) and the oxidation product (H-2 and CH_2). The rate constants were evaluated by table computer via the method of least squares. All results have correlation coefficients > 0.99.

The reactions were first order, both in the substrate and in the dihydropyridine. The observed rate constants presented in Table V are average values of three separate runs. To verify the structure of the saturated ketones **5a–c** and **6a–c**, the reaction mixtures were evaporated to dryness (50 °C, 15 mm) and the residue was redissolved in 5 mL of $CHCl_3$. To the resulting solution a 4 M excess of Na_4-EDTA, in 5 mL of distilled water, was added, the mixture was stirred for 5 min, and the $CHCl_3$ layer was separated. The aqueous layer was extracted with $CHCl_3$, and the combined $CHCl_3$ layers were washed with 5 mL of distilled water, dried overnight over sodium sulfate, and evaporated to dryness. Product analysis was carried out on the remaining residue by gas chromatography (20% SE-30, 0.5 m, 120 °C) and by IR and ^1H NMR spectroscopy. The reaction products were isolated in more than 80% yield. The products obtained upon reduction by 4,4-dideuterated **1** and **2** were fully deuterated at the carbon atom β to the carbonyl (^1H NMR). The assignments were straightforward (vide experimental data), except in the case of **6a**, where the ^1H NMR signals of $C(\alpha)H_2$ and $C(\beta)H_2$ overlap in the spectrum. In that case, the exact position of the deuterium atom was determined by reducing the monodeuterio **6a** to the corresponding monodeuterioalcohol **8a**, **3-(2-pyridyl)-1-phenyl-3-deuteriopropan-1-ol**: ^1H NMR ($CDCl_3$) C(OH)H 4.79 ppm (m, 1 H), $C(\beta)HD$ 2.96 ppm (m, 1 H), $C(\alpha)H_2$ 2.16 ppm (m, 2 H).

Results and Discussion

Recently, the conformation of (*E*)-2-cinnamoylpyridine (**3a**) in solution has been established by IR and ASIS (NMR) spectroscopy.[27] It has been found that (*E*)-**3a** has almost exclusively the N,O-trans conformation. In the presence of the metal ions, however, the repulsion between the free electrons of the pyridine nitrogen and those of the carbonyl oxygen, which is partly responsible for the N,O-trans conformation of free **3a**, is eliminated, and the N,O-cis structure, in which **3a** acts as a bidentate ligand, can become the preferred conformation. The data presented in Table III are in agreement with this suggestion. The negative shift of $\nu_{C=O}$ in the complexes **9a** and **9b**, combined with a positive shift of the pyridine breathing mode in both complexes, clearly indicates that **3a** coordinates with Zn(II) through its N and O sites simultaneously. The same phenomenon has been reported for related complexes.[28-30] The shift of $\nu_{C=C}$ to lower frequency in the complex can be regarded as further evidence for interaction of the metal with carbonyl oxygen. In **9a** the shifts of $\nu_{C=O}$ and $\nu_{C_\alpha=C_\beta}$ are smaller than in **9a**, thus reflecting the fact that the effective positive charge on the Zn atom is smaller in the case of the $ZnCl_2$ complex than in the $Zn(ClO_4)_2$ complex. The



9a 9b

Figure 2. Structures of $ZnCl_2$ and $Zn(ClO_4)_2$ complexes of 2-cinnamoylpyridine.

assignments of the far-IR spectral data, as presented in Table III, are based upon analogy with assignments made in the case of similar complexes.[28-34] The positive shift of the C(2)—C(=O) torsional vibration, its drop in intensity, and the direct observation of ν_{Zn-N} (in the case of both **9a** and **9b**) and ν_{Zn-O} (in the case of **9b**) can be regarded as additional evidence that **3a** acts as a bidentate ligand in both complexes. The observed Zn-Cl vibration in the far-IR spectrum of **9a,** coupled with the lack of evidence for a Zn(II)-perchlorate interaction in **9b,** supports the suggestion that the effective positive charge on the zinc atom is greater in complex **9b** with perchlorate as the counterion. Finally, the observation of a single Zn-Cl stretching vibration and a single Zn-N stretching vibration in the case of **9a** indicates a trans-planar octahedral structure for this complex, while two Zn-N and two Zn-O vibrations in the far-IR spectrum of **9b** are consistent with a tetrahedral structure (Figure 2). In the ^{13}C NMR spectra of the mixtures of enones (**3a-c, 4a-c**) and metal ions (Table IV), the C-3, C-4, and C-5 chemical shifts are indicators of the charge densities at these positions. From the data it would appear that charge withdrawal is largest in the case of **3a.** The effect of addition of Mg(II) on the spectra of **3b,c** and **4b,c** is smaller and essentially similar, while **4a** shows virtually no complexation. The upfield shift of C-2 and C-6 of the pyridine ring is striking. In the case of protonated pyridine, this has been interpreted as arising from a change in the order of the N-C bond upon protonation.[25] It has been suggested[26] that this effect is caused by a change in the electron distribution about C-2 and C-6, rather than a change in the net charge density. The fact that this upfield shift is also apparent upon addition of Mg(II) ions to the enones attests to the binding of the enones to the metal ion through the pyridine nitrogen. The large downfield shift of the carbon atom β to the carbonyl in **3a,** observed upon addition of metal ions, reflects a substantial charge withdrawal from this position. Since a similar large shift is absent in the case of the 3 or 4 isomer, this effect can be regarded as direct evidence for interaction of the metal ion with the carbonyl oxygen. The pattern of the chemical-shift displacements is in accordance with that expected on the basis of the known (alternating) effect of a charge on contiguously located atoms.[26] The comparison of the displacements upon addition of $Mg(ClO_4)_2$ and $Zn(ClO_4)_2$ shows that coordination of the ligand to the metal ion is of a similar nature. The difference in the displacement of the carbonyl carbon in the two cases presumably arises from unpredictable direct steric and field effects related to the proximity of the metal ions to this specific site.[26]

Reduction of α,β-Unsaturated Ketones by 1,4-Dihydropyridines. It has been shown that chalcone (1,3-diphenylprop-2-en-1-one) is inert to 1,4-dihydropyridines at room temperature,[36] while mixtures of azachalcones **3a-c** or **4a-c** and dihydropyridines (**1** or **2**) exhibit no change in the ^1H NMR spectra after 3 days (CD_3CN, room temperature), except for

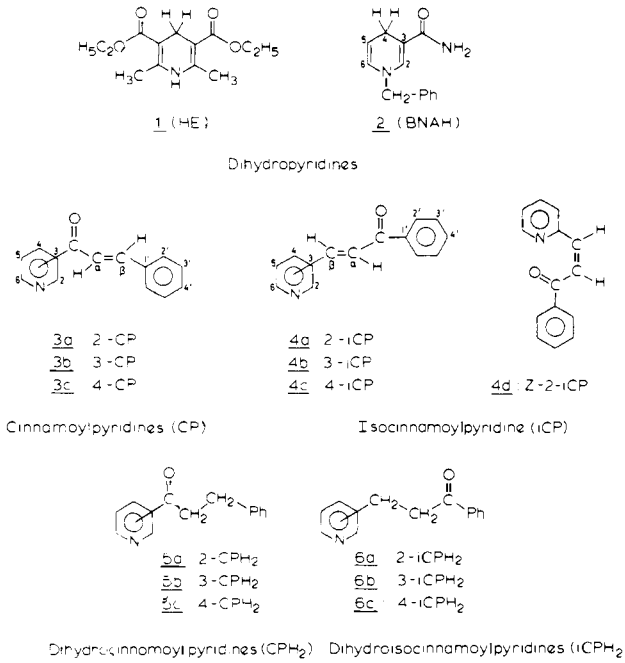
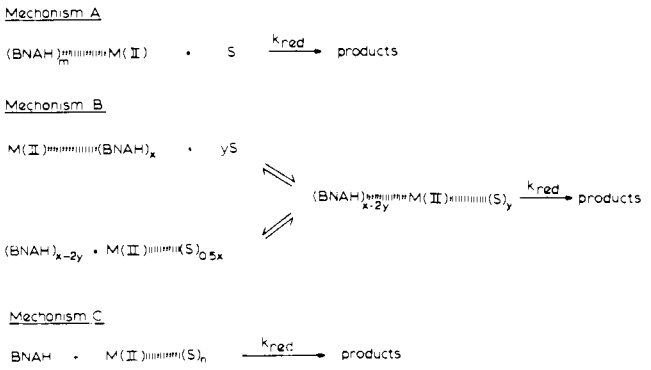


Figure 3. Dihydropyridine derivatives. Model substrates and their reduction products.

a slow decrease in intensity of the dihydropyridine signals. When, however, **3a-c** and **4a-c** are allowed to react with **1** or **2** in the presence of $Mg(ClO_4)_2$ or $Zn(ClO_4)_2$, they are smoothly reduced to the corresponding saturated ketones, **5a-c** and **6a-c,** respectively (Figure 3). When the 4,4-dideuterated analogues of **1** and **2** are employed as reducing agents, the number of gram atoms of deuterium, incorporated in the reduction products (**5a-c** and **6a-c**), is found to be approximately one (^1H NMR) in each case, the deuterium being incorporated at the carbon atom β to the carbonyl group.

Although for a rigorous analysis of the kinetic data it is necessary to correct by a factor that includes the effect of the association constants of the metal ion with the two reacting species, attempts to determine these constants have so far been unsuccessful, due to experimental limitation arising from the high extinction coefficients of the enones **3a-c** and **4a-d.** In order to determine these association constants, very high metal salts to enone concentration ratios have to be employed. Under these conditions, however, no isosbestic point can be identified in the UV spectra of the various enones with increasing metal ion concentrations. Despite the fact that these constants are not available, it is pertinent to note that the kinetic data, presented in Table V, show that the rates of reduction of **3a** are approximately 1600 and 300 times that of **3b** and **3c,** respectively. The observation that the reduction of **3b** and **3c** (which do not coordinate with the metal via the carbonyl oxygen) is facilitated by Mg(II) ions suggests that the metal ions do promote reduction by electronic effects arising from coordination with the nitrogen. The extra rate enhancement observed for the 2 isomer **3a** is, however, significant and suggests catalysis via direct coordination with the carbonyl oxygen to the metal ion. Similar results have been obtained with the $ZnCl_2$-catalyzed tetraethylammonium borohydride reduction of 2-, 3-, and 4-pyridinecarboxaldehyde.[7] The ketones **4a-c** form complexes with Mg(II) through their pyridine nitrogen alone, since simultaneous complexation with the N and O sites is sterically impossible. The observed second-order rate constants for **4a-c** (Table V) show a ratio of 5:2:6. These results are in agreement with the expected catalytic effect of the metal ions upon reductions via an inductive effect. It is noteworthy, that, although **4a** shows virtually no complexation with metal ions (NMR), addition of the latter does substantially catalyze

Scheme I. Mechanisms of Metal-Catalyzed Reduction of Substrate(s) by BNAH

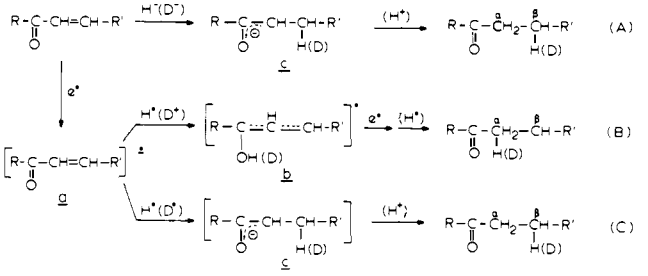


its reduction. In view of the fact that the saturated ketone **6a** exhibits a distinct coordination with the metal ions, it is suggested that similar coordination in the developing enolate anion or radical anion is implicated in the transition state involving the hydride or electron transfer from the reductant to the substrate. In contrast to the nondetectable coordination of **4a**,[35] the corresponding *Z* isomer **4d** was observed to show a significant shift of its protons upon addition of magnesium or zinc perchlorate. The data fulfil the anticipation that the metal ions should coordinate with both the N and O sites in **4d** to form a seven-membered ring. This coordination is reflected in the fact that **4d** is reduced 13 times faster than **4a** (Table V). The modest acceleration of the reduction of **4d** compared to that of **4a** is attributed to the relatively less effective complexation in the seven-membered ring.

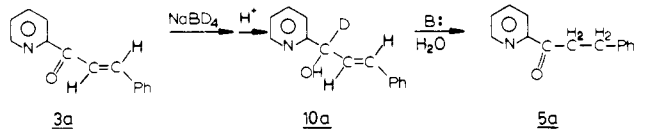
It has recently been suggested[37] that metal ion catalyzed reductions with 1,4-dihydropyridines involve a dihydropyridine–metal ion complex as the reactive species (Scheme I, mechanism A). The above-mentioned results can be rationalized in terms of a mechanism in which the substrate is activated toward the reduction process by complexation with metal ions. The detailed picture may involve a reaction within a ternary complex intermediate[38] (mechanism B) or a reaction between the complexed substrate species and the free dihydropyridine derivative (mechanism C[38c,39]).

Mechanism of Hydrogen Transfer. The kinetic deuterium isotope effect, determined by the use of BNAH-*4,4-d*$_2$, in the reduction of 2-CP is 3.10 ± 0.05. This value is indicative of hydrogen transfer in the rate-determining step. There is, at the moment, no consensus of opinion on the mechanism of the hydride-equivalent transfer from dihydropyridines to substrate systems.[40-46] Although it may be viewed as simply a one-step hydride transfer,[42] schemes involving sequential transfers of e + H′ and e + H$^+$ + e are possible in theory.[37,43] Evidence for free-radical intermediates has been presented in several cases.[44] In a recent study the involvement of one or more intermediates in the oxidation of 1-substituted 1,4-dihydropyridines[46] has been strongly supported. Reduction of the enones with 4,4-dideuterated 1,4-dihydropyridines leads to the corresponding saturated ketones containing one deuterium atom. Three possible reaction mechanisms, A, B, and C (Scheme II), can be suggested for the formation of these products. These involve (A) a hydride transfer, (B) an electron proton and an electron transfer, and (C) a sequential electron and hydrogen atom transfer. The transfer of a hydride to the unsaturated ketone system (mechanism A) should give the saturated ketone in which the deuterium label would be expected at the β carbon. In considering mechanisms B and C, it is expected that the radical anion intermediate a formed by addition of an electron to the substrate would undergo protonation (mechanism B) at the oxygen site to give intermediate b, while an addition of a hydrogen atom to the same (mechanism C) should result in anion c. As a consequence, upon completion of the reaction,

Scheme II. Mechanisms of Hydrogen Transfer to α,β-Unsaturated Ketones



Scheme III. Base-Catalyzed Isomerization of the $NaBD_4$ Reduction Product of 2-CP



the product obtained via mechanism B would be labeled at the α carbon and that found via mechanism C would carry the label at the β position. In light of the observation that all the unsaturated ketones are reduced to β-deuterated products, mechanisms A and C are both candidates for the reaction pathway.

In an attempt to synthesize deuterium-labeled **5a**, for comparison, **3a** was reduced with $NaBD_4$ according to a reported procedure.[47] The product of this reaction was, however, shown to be the monodeuterated allylic alcohol **10a** (Scheme III). This alcohol isomerizes under the influence of base to the saturated ketone **5a** *with the loss of deuterium.* The latter result indicates a 1,2-deuteride shift in the anion of **10a**, since the C-α deuterated product thus formed would be expected to undergo a loss of the label under the conditions of the reaction. A mechanism involving an initial double bond isomerization in **10a**, which would shift the label to C-β, is excluded by the observation that a deuterium label at the β position in **5a** is not lost under comparable conditions. Taken in conjunction with the fact that reduction of **3a** by **2**-*4,4-d*$_2$ leads to incorporation of the label at C-β, the forementioned results also show that a pathway involving an allylic intermediate is not operative in the reaction.

Recently, the mechanism of action of Δ⁴-3-ketosteroid reductases has been the subject of discussion.[48,49] While the reduction of an α,β-unsaturated ketone via its corresponding iminium salt has been shown to be feasible in model studies,[47] reduction of (3-oxo)-^{18}O-labeled Δ⁴-3-ketosteroid by 5α- and 5β-reductases has been found to involve retention of the label in the reduction product.[49] This result argues against the formation of an imine intermediate, in the enzymatic reaction (examined), and supports a mechanism in which the C=C—C=O system is activated by coordination of the carbonyl oxygen with an electrophile. The results obtained in the present study show that the metal ion catalyzed reduction of **3a** by **1** or **2** may be regarded as a model reaction for the mechanism of action of 5α- and 5β-Δ⁴-3-ketosteroid reductases. In this model the pyridine nitrogen may be considered equivalent to a basic center at the active site of the enzymes, which helps to bind the cation that serves as an electrophilic catalyst for the reduction process.

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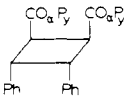

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