crystallization from water as a white solid, mp 170–171 °C dec. Anal. Calcd for $C_{11}H_8F_4N_4O_4$: C, 39.30; H, 2.40; N, 16.66. Found: C, 39.73; H, 2.10; N, 16.49.

Photolysis of Azide 4 in Cyclohexane. A 5.0×10^{-3} M solution of azide **4** in cyclohexane was photolyzed for 4.5 h. The crude photolysis mixture was separated by preparative TLC (3:2 $CHCl_3$–hexane) to give amine **35** (57%, R_f = 0.35), aniline **36a** (21%, R_f = 0.14), and azobenzene **37** (11%, R_f = 0.50). Amine **35**. ^{1}H NMR: δ 1.2 (m, 3), 1.3 (m, 2), 1.6 (m, 1), 1.76 (m, 2), 2.05 (m, 2), 3.6 (m, 1), 3.904 (s, 3), 4.02 (m, 1). Sublimation (60 °C/0.05 mm) gave the analytical sample of **35** as a colorless solid, mp 86–87 °C. Anal. Calcd for $C_{14}H_{15}F_4NO_2$: C, 55.08; H, 4.95; N, 4.59. Found: C, 55.28; H, 4.76; N, 4.48. Aniline **36a**: mp 113–114 °C (lit.[56] mp 116.5–117.0 °C). ^{1}H NMR: δ 3.916 (s, 3), 4.35 (s, 2). Azobenzene **37**. ^{1}H NMR: δ 4.032 (s). MS (rel intensity): 442 (44, M^+), 411 (23), 235 (70), 207 (100), 192 (30), 176 (50), 148 (52). High-resolution MS calcd for $C_{16}H_6F_8N_2O_4$ 442.0198, found 442.0200.

Photolysis of Azide 4 in Cyclohexane in the Presence of the Triplet Sensitizer Acetophenone. A 5.0×10^{-3} M solution of azide **4** in cyclohexane containing 5.0×10^{-2} M of acetophenone was photolyzed for 5 h. ^{1}H NMR of the crude photolysis mixture showed amine **35** (14%) and aniline **36a** (66%).

Photolysis of Azide 4 in Cyclohexane in the Presence of Diethylamine as Trapping Reagent. A 5.0×10^{-3} M solution of azide **4** in cyclohexane containing 5.0×10^{-2} M of diethylamine was photolyzed for 5 h. The crude photolysis mixture was separated by preparative TLC (2:1 $CHCl_3$–hexane) to give amine **35** (8%), aniline **36a** (24%), and hydrazine **38** (65%, R_f = 0.33). Hydrazine **38**. ^{1}H NMR: δ 1.105 (t, J = 6.9, 6), 2.753 (q, J = 6.9, 4), 3.916 (s, 3), 4.593 (s, 1). Sublimation (70 °C/0.05 mm) gave the analytical sample of **38** as a colorless solid, mp 94–95 °C. Anal. Calcd for $C_{12}H_{14}F_4N_2O_2$: C, 48.98; H, 4.80; N, 9.52. Found: C, 49.05; H, 4.63; N, 9.47.

Photolysis of Azide 4 in Toluene. A 4.0×10^{-3} M solution of azide **4** in toluene was photolyzed for 5 h. The crude photolysis mixture was separated by preparative TLC (2:1 $CHCl_3$–hexane) to give aniline **36a** (29%), amine **36b** (16%), **36c** (13%), and **36d** (9%). The structure of amine **36b–d** were established by reaction of the corresponding amine with ester **7** as described next.

Methyl *N*-Benzyl-4-aminotetrafluorobenzoate (36b). A solution of 130 mg of ester **7**, 90 mg of benzylamine, and 80 mg of Et_3N in 10 mL of CH_3CN was refluxed for 3 h. The solvent was evaporated, and the residue was dried by vacuum (0.05 mm, 25 °C). The solid was then sublimated (0.05 mm, 70 °C) to give 101 mg of **36b** as a white solid, mp 95–96 °C. ^{1}H NMR: δ 3.906 (s, 3), 4.478 (m, 1), 4.643 (d, J = 6.0, 2), 7.337 (m, 5). Anal. Calcd for $C_{15}H_{11}F_4NO_2$: C, 57.52; H, 3.54; N, 4.47. Found: C, 57.59; H, 3.53; N, 4.27.

Methyl *N*-(2-methylphenyl)-4-aminotetrafluorobenzoate (36c) and methyl *N*-(4-methylphenyl)-4-aminotetrafluorobenzoate (36d) were synthesized from ester **7** and the corresponding amines in a manner similar to **36b**. Amine **36c**: mp 110–111 °C; ^{1}H NMR: δ 2.328 (s, 3), 3.950 (s, 3), 5.620 (s, 1), 6.938 (d, J = 7.2, 1), 7.084 (t, J = 7.2, 1), 7.177 (t, J = 7.7, 1), 7.220 (d, J = 7.7, 1). Anal. Calcd for $C_{15}H_{11}F_4NO_2$: C, 57.52; H, 3.54; N, 4.47. Found: C, 57.96; H, 3.44; N, 4.58. Amine **36d**: mp 136–137 °C. ^{1}H NMR: δ 2.334 (s, 3), 3.948 (s, 3), 5.908 (s, 1), 6.914 (d, J = 8.0, 2), 7.127 (d, J = 8.0, 2). Anal. Calcd for $C_{15}H_{11}F_4NO_2$: C, 57.52; H, 3.54; N, 4.47. Found: C, 57.75; H, 3.31; N, 4.30.

Photolysis of Azide 4 in Toluene in the Presence of the Triplet Sensitizer Acetophenone. A 4.0×10^{-3} M solution of azide **4** in toluene containing 5.0×10^{-2} M of acetophenone was photolyzed for 5 h. ^{1}H NMR of the crude photolysis mixture showed aniline **36a** (62%) and amine **36b** (8%). No **36c** and **36d** were observed.

Photolysis of Azide 19 in Toluene. Photolysis of azide **19** and separation of the reaction mixture were carried out in a manner similar to azide **4** except that the photolysis time was 1.5 h. Aniline **39a** (71%, R_f = 0.21), mp 116–117 °C. ^{1}H NMR: δ 3.893 (s, 3), 4.52 (m, 2). Anal. Calcd for $C_8H_5F_3N_2O_4$: C, 38.41; H, 2.01; N, 11.20. Found: C, 38.29; H, 1.90; N, 10.86. Amine **39b** (8%, R_f = 0.27). ^{1}H NMR: δ 3.878 (s, 3), 4.660 (s, 2), 5.61 (sb, 1), 7.33 (m, 5). MS (rel intensity): 340 (20, M^+), 309 (5), 91 (100). High-resolution MS calcd for $C_{15}H_{11}F_3N_2O_4$ 340.0668, found 340.0670.

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Supplementary Material Available: Tables of the ^{19}F NMR spectral data for 1,4-disubstituted compounds **2–5**, **8–15b**, and **35–38** and trisubstituted compounds **16–19**, **21–23**, **27–29**, and **39a–b** and ^{1}H NMR (300 MHz) spectra of compounds **10**, **14**, **15b**, **23**, **37**, and **39b** (8 pages). Ordering information is given on any current masthead page.

Metal–1,10-Phenanthroline-Linked Dihydronicotinamides as Models for the NADH–Alcohol Dehydrogenase Coenzyme–Enzyme Couple

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Two phenanthroline-linked dihydronicotinamides, 1,4-dihydro-1-(1,10-phenanthrolin-2-ylmethyl)-3-pyridinecarboxamide (**3**) and 1,4-dihydro-*N*-(1,10-phenanthrolin-2-ylmethyl)-1-(phenylmethyl)-3-pyridinecarboxamide (**6**), were synthesized. The phenanthroline moiety in these compounds is able to chelate metal ions into fixed positions toward the dihydronicotinamide group providing models for the NADH–alcohol dehydrogenase complex. The reactivity of **3**–M^{2+} and **6**–M^{2+} is investigated toward 2,4,6-trinitrobenzene sulfonate and methylene blue (M^{2+} = Zn^{2+}) and toward the metallophilic substrate 2-pyridinecarboxaldehyde (PyCHO) for which a detailed kinetic analysis is given. For reaction of **3**–M^{2+} and PyCHO the efficiency of metal ion activation is of the order $Zn^{2+} \gg Mg^{2+}$, $Ni^{2+} > Co^{2+} > Cd^{2+}$. It is concluded that hydride transfer proceeds in a ternary **3**–M^{2+}–PyCHO complex in an orientation in which carbonyl group and dihydropyridine are in a coplanar position with the carbonyl oxygen pointing to the ring nitrogen.

The enzyme alcohol dehydrogenase is one of the dehydrogenases that utilizes zinc ion at the active site as a catalytic group. It catalyses the transfer of a hydride equivalent from the coenzyme NADH to a large variety of aliphatic and aromatic aldehydes and ketones and reverse. Alcohol dehydrogenase from horse liver, human liver, rat liver, yeast, and bacillus have been extensively studied and characterized, both by X-ray and chemical

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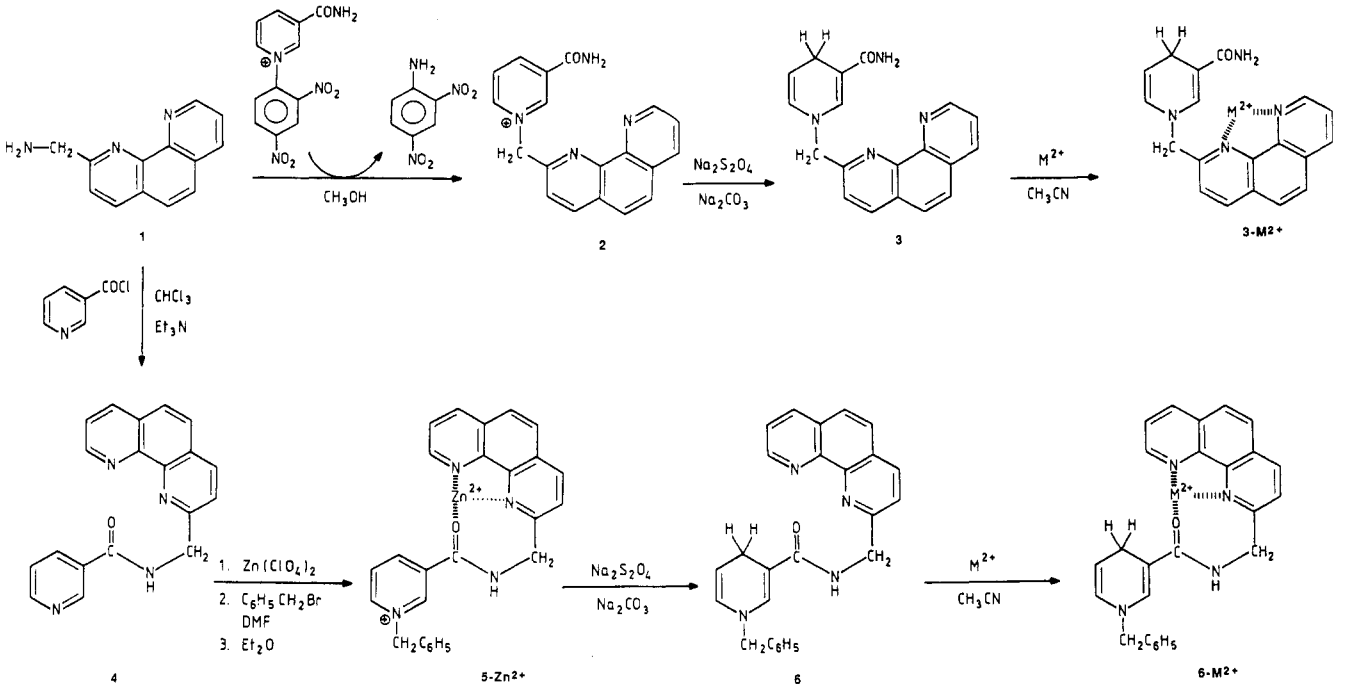
Scheme I



methods.[1,2] Several mechanisms have been considered for their catalytic action, most of them include binding of the substrate with its carbonyl oxygen coordinated to the zinc atom at the active site of the enzyme.[2a] Such coordination supposes that zinc acts as a Lewis acid, and, consequently, considerable efforts have been paid to elucidate the role of zinc and other metal ions in model reactions.[3] However, studies of reactions with NADH model compounds, mostly relatively simple 1,4-dihydropyridines, and various carbonyl compounds have yielded a diverse and contradictory picture about the role of the metal ion.[3-7] Reactions of NADH models with thiopivalophenone show inhibition upon addition of metal ion;[5] with methyl benzoylformate, trifluoroacetophenone, and certain diketones metal ion catalysis with kinetic saturation is observed,[6] and catalysis to an optimum metal ion concentration is observed for the reaction with 2-acylpyridines and 1-acylisoquinolines.[7] Much of the uncertainty in the interpretation of kinetic effects is caused by the fact that relative orientation of substrate, metal ion, and dihydronicotinamide group is not known. In order to circumvent this problem we have synthesized the NADH models **3**-M^{2+} and **6**-M^{2+}, (M^{2+} = Zn^{2+}, Co^{2+}, Ni^{2+}, Mg^{2+}, and Cd^{2+}), which contain a dihydronicotinamide group and a phenanthroline group chelating a metal ion in a fixed position. Both models bind the metal ion in close proximity to the nicotinamide group, similar to the active site of the alcohol dehydrogenase–NADH complex where van der Waals contact between active site zinc ion and nicotinamide have been established.[2e] It was the purpose of this study to examine whether the metal ion in these models could mimic the function of catalytic zinc in alcohol dehydrogenase, i.e. bind the substrate in the neighborhood of the dihydronicotinamide by coordination to the carbonyl oxygen, orient the dihydronicotinamide group and carbonyl group properly for transfer of a hydride equivalent, and activate the carbonyl group sufficiently for reduction. Most of our attention has been paid to model **3**-Zn^{2+}, which indeed shows good reactivity toward the metallophilic substrate 2-pyridinecarboxaldehyde.[8] The kinetic results prove that hydride transfer takes place inside a ternary complex analogous to the biological reduction.

Results

The model compounds **3** and **6** were prepared as shown in Scheme I. The molecules were characterized by ^1H NMR, UV–vis, and elemental analyses. In the absorption spectra of **3** and **6** the phenanthroline moiety has a maximum at 267 nm and the dihydronicotinamide part of the molecule shows a broad absorption band in the 320–400-nm region. Addition of 1 equiv of zinc perchlorate shifts the maximum from 267 to 275 nm, and a shoulder at 295 nm appears. These changes are characteristic for binding

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Scheme II

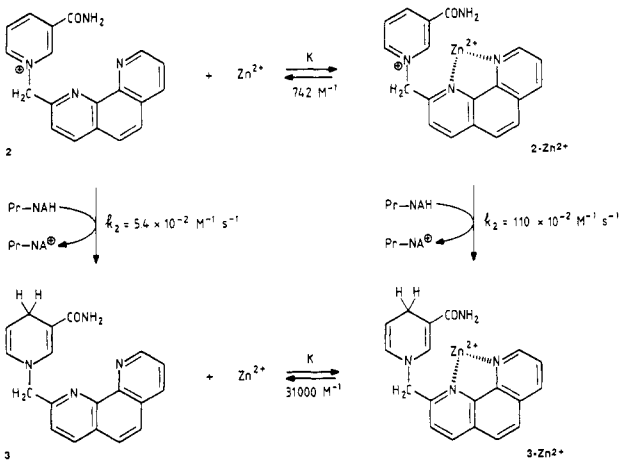

Table I. Second-Order Rate Constants[a] for the Oxidation of 3, 3-Zn^{2+}, 6, 6-Zn^{2+}, and BNAH by 2,4,6-Trinitrobenzenesulfonate (TNBS) and Methylene Blue (MB^+) at 25 °C

dihydronicotinamide[b]	TNBS,[c] k_2, M^{-1} s^{-1}	MB^+,[d] k_2, M^{-1} s^{-1}
3	0.897 ± 0.011	8.54 ± 0.06
3-Zn^{2+}	0.484 ± 0.004	5.12 ± 0.05
6	0.080 ± 0.002	14.8 ± 0.2
6-Zn^{2+}	0.106 ± 0.002	9.93 ± 0.05
BNAH	1.60 ± 0.02	41.7 ± 0.3

[a] Calculated from pseudo-first-order rate constants. [b] Initial concentration in the sample solution is 1.32×10^{-4} M. [c] Reaction in CH_3CN/H_2O (1:10 v/v) with [TNBS] = 5.0×10^{-3} M. [d] Reaction in CH_3CN/H_2O (1:1 v/v) with [MB^+] = 6.75×10^{-6} M.

of metal ion to the phenanthroline ring.[9] In the high-wavelength region the absorption near 360 nm decreases, suggesting that the phenanthroline-bound metal ion interacts with the dihydronicotinamide group. Molecular models show that ring nitrogen and π-system of the dihydronicotinamide group are able to come into van der Waals contact with the metal ion. Similar absorbance changes are obtained for Co^{2+}, Ni^{2+}, and Cd^{2+} bound to phenanthroline group.

It may be anticipated that binding of a metal ion to **3** and **6** is of direct influence on the reactivity of the dihydronicotinamide moiety, i.e. its intrinsic reactivity will be reduced by inductive electron withdrawal and spatial interaction of the metal ion. In order to obtain quantitative insight into the intrinsic reactivities of **3** and 3-Zn^{2+}, we have determined first their rate of formation from the corresponding pyridinium salts, **2** and 2-Zn^{2+}, in the transhydrogenation reaction[10] with 1-*n*-propyl-1,4-dihydronicotinamide (*n*-PrNAH) in methanol (Scheme II). Due to the presence of zinc ion in 2-Zn^{2+}, this compound reacts ca. 20 times faster in the formation of dihydronicotinamide than does **2**. Also, binding constants of zinc ion to **2** and **3** were determined, and, as expected, the dihydronicotinamide **3** has a significant higher affinity for Zn^{2+} than has **2**.

Next, the reactivity of **3**, 3-Zn^{2+}, **6**, and 6-Zn^{2+} were determined in comparison with that of the well-studied NADH model 1-benzyl-1,4-dihydronicotinamide (BNAH) in reactions with substrates which react in a direct bimolecular reaction, i.e. in which ternary complex formation is not part of the reaction pathway. Rate constants for reactions with the anionic substrate 2,4,6-trinitrobenzene sulfonate (TNBS)[11] and the cationic substrate methylene blue (MB^+)[12] as hydride acceptor are given in Table I. Comparison of the reactivities of **3** and 3-Zn^{2+} shows that binding of zinc ion reduces the reactivity of the dihydronicotinamide moiety, both to anionic and cationic substrates by ca. 60%. For 6-Zn^{2+}, the presence of zinc ion causes a small enhancement of the reaction rate with TNBS and a small decrease of the reaction rate with MB^+. This is in accordance with the expected effect of electrostatic interactions between the zinc-bound phenanthroline group and the charge of the substrates. Both model compounds **3** and **6** have a lower reactivity than has BNAH toward the substrates.

Table II. Apparent Second-Order Rate Constants, k_2^a, for the Reaction of 3-M^{2+}, 6-M^{2+}, and BNAH with PyCHO at 25 °C[a]

	k_2^a, M^{-1} s^{-1}		
M^{2+}	3-M^{2+}	6-M^{2+}	BNAH
Zn^{2+}	49.8 ± 1.4	1.65 ± 0.05	12.3 ± 0.2
Zn^{2+}	30.7 ± 1.0[b]		
Mg^{2+}	4.30 ± 0.04	0.86 ± 0.03	
Ni^{2+}	4.10 ± 0.07	2.21 ± 0.02	
Co^{2+}	2.79 ± 0.08	0.58 ± 0.02	
Cd^{2+}	1.57 ± 0.02		

[a] Conditions: Concentration of **3**, **6**, BNAH, and PyCHO in $CH_3CN/CHCl_3$ (95:5 v/v) solutions is 2.52×10^{-4} M. To **3** and BNAH 1 equiv and to **6** 2 equiv of $M(ClO_4)_2 \cdot 6H_2O$ are added. [b] Value for monodeuterio **3**, see text.

The most important function of the metal ion bound to the phenanthroline nucleus would be to serve as a template for substrate binding and orient and activate the substrate properly for reduction inside a ternary complex. Previous studies have revealed that 2-pyridinecarboxaldehyde (PyCHO) is activated by metal ions for reduction by dihydronicotinamides.[4g,h,7c] It is a suitable substrate for our purpose since metal ion binding occurs at a definite position involving the pyridine nitrogen and the carbonyl oxygen (at least in the transition state). In this way we have a system in hand in which relative positions of dihydronicotinamide group, metal ion, and substrate are defined. PyCHO does not react with **3** and **6** in the absence of metal ion, but addition of 1 equiv of metal ion as the perchlorate salt to **3** promotes the reaction in the order $Zn^{2+} \gg Mg^{2+}$, $Ni^{2+} > Co^{2+} > Cd^{2+}$. No reactivity is observed with the isomeric 3- and 4-pyridinecarboxaldehydes. For **6**, addition of more than 1 equiv of metal salt is necessary to induce reaction with PyCHO. Moreover, this reaction proceeds much more slowly than that of 3-Zn^{2+}. Table II collects the apparent second-order rate constants for reaction of **3** and **6** with PyCHO. For comparison, the reactivity of BNAH under these conditions was also determined.

It has been reported that 1,4-dihydronicotinamides are sensitive to addition to the 5,6-double bond in the presence of electrophilic species as hydronium ion,[13a] trifluoroacetophenone,[13b] and PyCHO-Zn^{2+} [13c] in aqueous solution. However the occurrence of this reaction seems to be dependent on the solvent, since no adduct formation between

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Table III. Effect of PyCHO Concentration on the Rate of Reaction with 3-M^{2+} (2.52×10^{-4} M) in $CH_3CN/CHCl_3$ (95:5) at 25 °C

	10^3k_{obsd}, s^{-1}		
10^3[PyCHO], M	3-Zn^{2+}	3-Ni^{2+}	3-Co^{2+}
1.5		4.7 ± 0.3[b]	2.34 ± 0.06
2.0	75 ± 6[a]	5.4 ± 0.2[b]	2.90 ± 0.08
2.5		6.1 ± 0.3[b]	3.71 ± 0.04
5.0	78 ± 5[a]	7.5 ± 0.2[b]	5.15 ± 0.06
7.5	78 ± 6[a]	8.1 ± 0.2[b]	6.70 ± 0.15
10.0	78 ± 5[a]	8.2 ± 0.2[b]	7.8 ± 0.2[c]
15.0			8.0 ± 0.2[c]

[a] Initial rate constant (0–5 s). [b] Initial rate constant (0–60 s). [c] Initial rate constant (0–120 s).

PyCHO-Zn^{2+} and dihydronicotinamide moiety have been observed in acetonitrile[13c] and in 2-propanol.[14] In order to confirm that reduction of PyCHO is the process that is kinetically observed under our conditions, we have recorded the absorption spectra of an equimolar solution of 3-Zn^{2+} (2.52×10^{-4} M) in acetonitrile at 5-s time intervals with a diode array spectrophotometer in the range 250–500 nm. These spectra show that the decrease of the absorption in the range 290–400 nm is accompanied by an increase in the range 250–270 nm, corresponding to the conversion of the dihydronicotinamide moiety (λ_{max} = 360 nm) to the quaternary nicotinamide (λ_{max} = 265 nm). No increase in absorption is observed in the region near 290 nm, where 5,6-adducts of 1,4-dihydronicotinamides have a maximum.[13] Analysis of the reaction on 0.5-mmol scale with TLC, ^1H NMR, and GC–MS shows that the reaction products are 2-pyridylmethanol and **2**. Furthermore, addition of more than 1 equiv of metal ion to a solution of 3-M^{2+} and PyCHO gives a *decrease* in the rate of disappearance of the dihydronicotinamide absorption. Addition of metal ion to a PyCHO solution results in increment of the concentration of PyCHO-M^{2+} at the expense of free PyCHO. If adduct formation would significantly contribute to the reaction, an increase in rate of disappearance of the dihydronicotinamide absorption should have been observed upon increase of the concentration of electrophilic PyCHO-M^{2+}. In contrast, for the redox process the observed decrease in rate can be ascribed to the decrease of the concentration of free PyCHO in solution which can form a ternary complex with 3-Zn^{2+} in which the redox reaction occurs. Reaction of PyCHO with monodeuterio 3-Zn^{2+}, in which one of the C-4 hydrogens of the dihydronicotinamide is substituted by deuterium gives an apparent second-order rate constant k_2^a(HD) = 30.7 ± 1.0 M^{-1} s^{-1}. This yields a kinetic isotope effect $k_2^a(HH)/k_2^a(HD)$ = 49.8 ± 1.4/30.7 ± 1.0 = 1.62 (±0.07). On the assumption that the contribution of the secondary isotope effect is small a primary isotope effect k_H/k_D = 4.3 can be calculated.[12] This points out that hydrogen transfer is part of the rate-limiting step.[15]

The kinetics of the reaction of 3-M^{2+} have been examined in more detail by variation of the concentration of PyCHO and the metal ion. Table III gives the pseudo-first-order rate constants, k_{obsd}, for reaction of 3-Zn^{2+}, 3-Ni^{2+}, 3-Co^{2+} (2.52×10^{-4} M) with PyCHO in large excess. In these reactions the problem arises that excess of PyCHO deprives the phenanthroline moiety of its metal ion, and this results in inactivation of the dihydronicotinamide models. This becomes apparent in a rapid decrease of the initial reaction rate which is most distinct for 3-Zn^{2+} and less for 3-Ni^{2+} and 3-Co^{2+} and reflects the relative affinities of **3** and PyCHO for these metal ions. The data in Table III show that 3-Zn^{2+} is the most reactive model and that estimated initial rates are almost independent of the PyCHO concentration. Increase of [PyCHO] in reactions of 3-Ni^{2+}, and 3-Co^{2+} exhibits saturation kinetics. In contrast, increment of [PyCHO] in a solution of 6-Zn^{2+} (2.52×10^{-4} M) and zinc perchlorate (5.04×10^{-4} M) has little effect on the reaction rate.

Table IV. Pseudo-First-Order Rate Constants for the Reaction of 3-Zn^{2+} (2.52×10^{-4} M) with PyCHO in Excess in the Presence of Zinc Perchlorate in $CH_3CN/CHCl_3$ (95:5 v/v) at 25 °C.

	10^3k_{obsd}, s^{-1}, for $[Zn(ClO_4)_2 \cdot 6H_2O]$		
10^3[PyCHO], M	1.0×10^{-2} M	2.0×10^{-2} M	4.0×10^{-2} M
5.0	38.0 ± 0.3	18.9 ± 0.3	10.5 ± 0.2
7.5	56.5 ± 0.3	28.5 ± 0.3	15.5 ± 0.2
10.0	75.3 ± 0.8	38.0 ± 0.6	21.0 ± 0.3
15.0	97.1 ± 1.5	57.0 ± 0.9	30.5 ± 0.1
20.0	128 ± 1.7	77.4 ± 1.4	40.5 ± 0.5
25.0	150 ± 2.6	98.6 ± 2.0	51.0 ± 1.1

Table V. Effect of Zinc Salt Concentration and Water Concentration on the Rate of Reduction of PyCHO (10^{-2} M) by 3-Zn^{2+} and 6-Zn^{2+} (2.52×10^{-4} M) in $CH_3CN/CHCl_3$ (95:5 v/v) at 25 °C

	10^3k_{obsd}, s^{-1}		
10^3[zinc salt], M	3-Zn^{2+} ($Zn(ClO_4)_2 \cdot 6H_2O$)	3-Zn^{2+} ($ZnBr_2$)	6-Zn^{2+} ($Zn(ClO_4)_2 \cdot 6H_2O$)
0.0	78 ± 5[a]		
0.5	85 ● 3[a]		
1.0	101 ± 7[a]	1.5 ± 0.1	
2.0	118 ± 2	2.1 ± 0.1	
3.0	118 ± 2	2.6 ± 0.1	5.2 ± 0.2
5.0	115 ± 3	3.2 ± 0.2	9.3 ± 0.2
5.0 + 30 mM H_2O	114 ± 3	3.3 ± 0.1	
5.0 + 60 mM H_2O	109 ± 3	3.6 ± 0.1	
5.0 + 90 mM H_2O	103 ± 4		
5.0 + 120 mM H_2O	100 ± 2		
7.5	100 ± 2	3.6 ± 0.2	20.2 ± 0.6
10.0	75 ± 1	3.7 ± 0.2	33.0 ± 0.5
15.0	55 ± 2	3.7 ± 0.1	
20.0	38 ± 1	3.7 ± 0.1	
25.0	32 ± 2	3.6 ± 0.1	
30.0	28 ± 1	3.5 ± 0.1	
40.0	21 ± 1	3.3 ± 0.2	
50.0	17 ± 1	3.3 ± 0.2	

[a] Initial rate constant (0–10 s).

In order to avoid loss of zinc ion from 3-Zn^{2+} upon increment of [PyCHO], this reaction was also studied in solutions of zinc perchlorate of 1.0, 2.0, and 4.0×10^{-2} M, respectively. In these solutions excess of zinc ion acts as buffer so that formation of PyCHO·Zn^{2+} species does not deprive 3-Zn^{2+} from its zinc ion. Accordingly, also at higher [PyCHO] the reaction maintains pseudo-first-order kinetics. The k_{obsd} values are given in Table IV. It is important to note that increase of the zinc perchlorate concentration decreases the rate of reaction. This implies that an equilibrium shift from free PyCHO to PyCHO·Zn^{2+} species has an inhibitory effect on the reaction, pointing out that it is free PyCHO rather than PyCHO·Zn^{2+} that is reduced by 3-Zn^{2+}. Furthermore, the k_{obsd} values in Table IV show that for zinc perchlorate concentrations of 4.0×10^{-2} and 2.0×10^{-2} M increment of [PyCHO] results in an almost proportional increase of k_{obsd}. In 1.0×10^{-2} M zinc perchlorate solution the increment of k_{obsd} is leveled off at high [PyCHO], indicating that a ternary 3-Zn^{2+}–PyCHO complex becomes formed to saturation.

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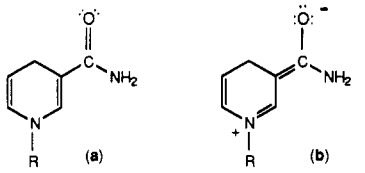


Figure 1. Resonance forms of dihydronicotinamide.

The effect of variation of the concentration of zinc salt was further examined for 3-Zn^{2+} at fixed [PyCHO] of 10^{-2} M. The results are given in Table V. At low concentration of zinc perchlorate the initial rate gradually increases due to diminished loss of zinc ion from 3-Zn^{2+}, but further increment of the zinc perchlorate concentration causes a gradual decrease of the reaction rate, in agreement with the decrease of free PyCHO species in solution. Futhermore, addition of small amounts of water to the zinc perchlorate solution does have only minor effects. Remarkably, the effect of zinc bromide on the reaction rate is very different from that of zinc perchlorate, since the reaction proceeds much slower and increment of the zinc bromide concentration yields a rate effect *opposite* to that of zinc perchlorate. These effects cannot be caused by differences in water content in both solutions, since addition of 6 equiv of water to the zinc bromide solutions causes no significant increase of the reaction rate. Apparently, differences in degree of dissociation of both salts are responsible for the observed effect. Zinc perchlorate is much better dissociated in acetonitrile than is zinc bromide[7c] and consequently complexation of PyCHO to 3-Zn^{2+} will proceed better with perchlorate than with bromide as the counterion.

Discussion

In the NAD-alcohol dehydrogenase complex van der Waals contact between nicotinamide ring and zinc ion at the active site have been established from X-ray data.[2e] In the model compounds 3-M^{2+} and 6-M^{2+} the metal ion bound to the phenanthroline group interacts with nitrogen and/or π-system of the dihydronicotinamide moiety. This is apparent from the downfield shift of the dihydronicotinamide protons in the ^1H NMR spectrum (see Experimental Section) and from the change in the absorbance spectrum in the 300-450-nm region upon addition of 1 equiv of metal ion. The decrease of the absorption in the 340-nm region may be attributed to less favorable contribution of resonance form b in Figure 1 to the electronic transition due to the vicinity of the metal ion. From the spectral changes it appears that coordination with the carboxamide oxygen does not occur since this type of coorindation would promote the electronic transition and lower the energy, leading to a shift to longer wavelength. This is indeed what is observed upon addition of zinc perchlorate to BNAH, which causes a concomitant increase and shift of the absorbance maximum from 346 to 366 nm.[7c] For BNAH, binding of zinc ion to the carboxamide oxygen has been established by ^1H and ^{13}C NMR spectroscopy.[7d] Molecular models of 3-Zn^{2+} and 6-Zn^{2+} reveal that the dihydronicotinamide ring is geometrically in a much better position than is the carboxamide oxygen to bind to tetrahedrally coordinated zinc. The faster rate of formation of the dihydronicotinamide in the presence of zinc ion in the transhydrogenation of **2** with Pr-NAH and the larger binding constant of Zn^{2+} for **3** than for **2** also suggests that zinc ion interacts favorably with the dihydronicotinamide group. Additional support is obtained by the lower reactivity of 3-Zn^{2+} toward TNBS and MB^+, respectively. Both **3** and **6** have a significant lower reactivity than has BNAH in these reactions. However, with PyCHO as the substrate, 3-Zn^{2+} is 4 times more reactive than is BNAH in the presence of 1 equiv of zinc ion. This larger reactivity must be due to the ability of 3-Zn^{2+} to bind PyCHO in a ternary complex in which hydride transfer can take place easily. Zinc ion is the most powerful activator of the reduction process, but other metal ions tested, Mg^{2+}, Ni^{2+}, Co^{2+}, and Cd^{2+}, also exhibit activity. However, the presence of the metal ion bound to the phenanthroline moiety in 3-M^{2+} is essential to achieve reduction of PyCHO. This is also illustrated by the kinetic behavior upon increasing PyCHO concentration. In the presence of large excess of PyCHO the initial rate is rapidly slowed down due to loss of metal ion from 3-M^{2+} to PyCHO. The attendant formation of PyCHO-M^{2+} clearly cannot compensate the decrease of reactive 3-M^{2+} species in solution, indicating that it is not PyCHO-M^{2+} which reacts with the dihydronicotinamide group. This is confirmed by inhibition of the reaction when the zinc perchlorate concentration is increased, as is shown in Tables IV and V. Since increment of zinc perchlorate concentration results in increase of [PyCHO·Zn^{2+}], an enhanced rate would be observed if this species was substrate for reduction.

Table VI. K_m and k_c Values for the Reaction of PyCHO with 3-Zn^{2+}, 3-Co^{2+}, and 3-Ni^{2+} in $CH_3CN/CHCl_3$ (95:5 v/v) at 25 °C

	3-Zn^{2+}	3-Co^{2+}	3-Ni^{2+}
K_m, mM	2.20 ± 0.10	5.91 ± 0.20	1.88 ± 0.10
$10^3 k_c$, s^{-1}	100 ± 10	11.4 ± 1.0	10.5 ± 1.0

A reaction scheme which accounts for the observed kinetic effects is presented in eqs 1-3. Equation 1 gives the reduction of PyCHO by 3-M^{2+} after the preliminary formation of a ternary 3-M^{2+}-PyCHO complex. Equation 2 shows the inhibition of the reaction by the presence of excess of metal ion and eq 3 accounts for the decline of reaction rate when large excess of PyCHO is added to 3-M^{2+}.

$$3\text{-}M^{2+} + PyCHO \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PyCHO\cdot M^{2+}\cdot 3 \xrightarrow{k_c} PyCH_2O^- - M^{2+} - 2 \quad (1)$$

$$PyCHO + M^{2+} \underset{}{\overset{K_i'}{\rightleftharpoons}} PyCHO\cdot M^{2+} \overset{K_i'[PyCHO]}{\rightleftharpoons} (PyCHO)_2 M^{2+} \quad (2)$$

$$3\cdot M^{2+} + 2PyCHO \xrightarrow{k_i} 3 + (PyCHO)_2M^{2+} \quad (3)$$

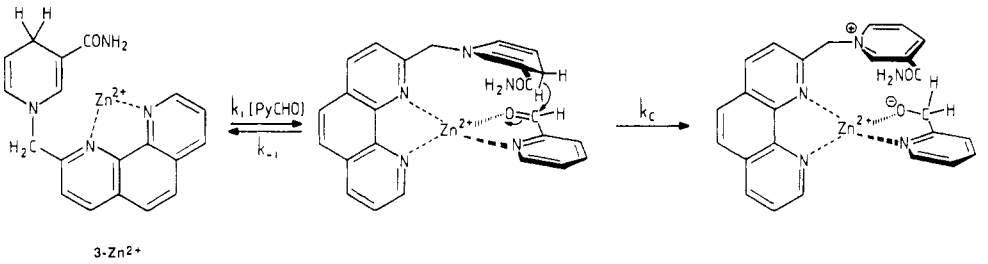
From eq 1, expression 4, related to the Michaelis Menten equation, can be derived, where [PyCHO] is the concentration of *free* PyCHO in solution and $K_m = (k_{-1} + k_c)/k_1$.

$$k_{obsd} = \frac{k_c[PyCHO]}{K_m + [PyCHO]} \quad (4)$$

This equation explains the experimental behavior since at low concentrations of free PyCHO, where $K_m \gg$ [PyCHO], the reaction shows first-order dependence on [PyCHO]. For reactions where [PyCHO] $\gg K_m$ the reaction rate reaches a limiting maximum value with $k_{obsd}(max) = k_c$. This behavior is observed for reactions of 3-Ni^{2+} and 3-Co^{2+} which show maxima in their initial rates upon increasing [PyCHO]. K_m and k_c can be evaluated by rearrangement of eq 4 into the reciprocal form which gives linear plots of $1/k_{obsd}$ vs 1/[PyCHO] with slope K_m/k_c and intercept $1/k_c$ for 3-Ni^{2+} and 3-Co^{2+} (Table VI).

However, 3-Zn^{2+} looses its catalytically active zinc ion too readily when PyCHO is present in large excess.

Scheme III



3-Zn^{2+}

Therefore additional zinc perchlorate was added. In these solutions binding of PyCHO to the metal ion is competitive with complexation to 3-M^{2+} and consequently is inhibitory to the reduction reaction. Therefore eq 2, which relates the concentration of free PyCHO to the concentration of M^{2+} in solution, has to be included in the kinetic expression, yielding[8] for the concentration range where $[PyCHO]_t < [Zn^{2+}]$ eq 5, which shows that k_{obsd}^{-1} should be linear

$$\frac{1}{k_{obsd}} = \frac{K_m K'_i}{k_c} \frac{[M(ClO_4)_2]_t}{[PyCHO]_t} - \frac{K_m K'_1}{k_c} + \frac{1}{k_c} \qquad (5)$$

with $[M(ClO_4)_2]_t$ and $[PyCHO]_t^{-1}$ (Figure 2). From this equation for $K_m K'_i/k_c$ = 11.0 (±1.0) s and for k_c = 100 (±10) × 10^{-3} s^{-1} is calculated.

K_m can be calculated if K'_i is known. Unfortunately, this binding constant could not be determined from the change in the absorption spectrum of PyCHO upon increment of the zinc perchlorate concentration, since the formation of $(PyCHO)_2 \cdot Zn^{2+}$ species complicates the spectral changes at low concentration of metal ion. Therefore, K_m for 3-Zn^{2+} was calculated from the apparent second-order rate constant, $k_2^{app} = k_c/K_m$, yielding K_m = 2.20 mM. Values for K_m and k_c for 3-Zn^{2+}, 3-Co^{2+}, and 3-Ni^{2+} are given in Table VI. The data in this table show that the highest reactivity of 3-Zn^{2+} is both caused by the largest affinity of PyCHO toward zinc and by the largest rate of reduction inside the ternary complex. 3-Ni^{2+} and 3-Co^{2+} bind PyCHO less strongly and also possess a lower potency to activate the carbonyl group for reduction.

For 6-Zn^{2+}, binding of PyCHO to the phenanthroline-bound zinc ion is not followed by hydride transfer. This can be concluded from the facts that more than 1 equiv of zinc perchlorate is necessary to start reaction and that further increment of the zinc perchlorate concentration (which gives rise to increase of $PyCHO \cdot Zn^{2+}$ concentration), enhances the reaction rate. Apparently, the 6-Zn^{2+}-PyCHO complex has not the proper geometry requirements to bind PyCHO in a ternary complex that is able to transfer the hydride efficently. Reduction of PyCHO-Zn^{2+} by 6-Zn^{2+} then has to proceed by a bimolecular pathway. For the ternary complex 3-Zn^{2+}-PyCHO, however, CPK models show that the C-4 hydrogens of the dihydronicotinamide group can easily make van der Waals contact with the carbon atom of the carbonyl group of PyCHO. Hydride transfer in this complex can proceed with a favorable dipole orientation in which the carbonyl oxygen is pointed to the ring nitrogen of the dihydronicotinamide group (Scheme III). This orientation is also suggested for carbonyl reduction at the active site of alcohol dehydrogenase[16] and has been used to explain the stereochemistry of enzymatic carbonyl reductions.[17,3d,4d]

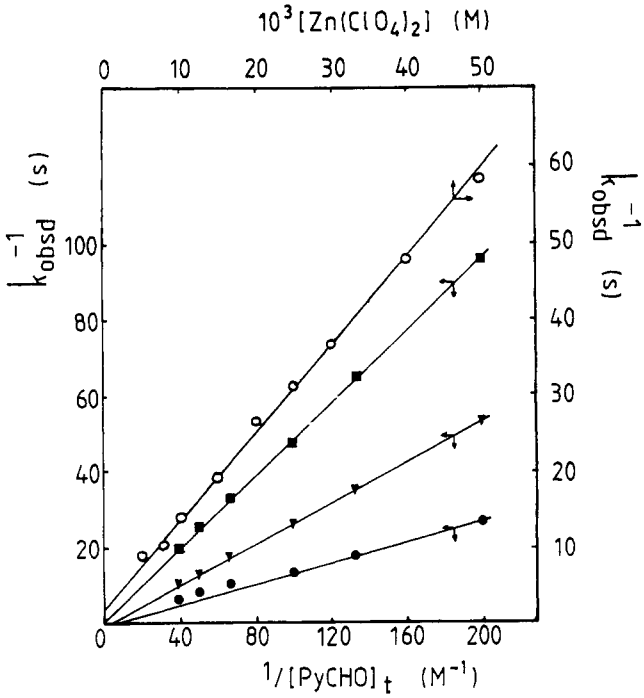


Figure 2. Plot of $1/k_{obsd}$ vs $1/[ZnClO_4]_t$ for the reaction of 3-Zn^{2+} with 10^{-2} M PyCHO (○) and of $1/k_{obsd}$ vs $1/[PyCHO]_t$ for the reaction of 3-Zn^{2+} with PyCHO at $[Zn(ClO_4)_2 \cdot 6H_2O]$ = 1.0 × 10^{-2} M (●); 2.0 × 10^{-2} M (▼), and 4.0 × 10^{-2} M (■).

Experimental Section

Materials. Metal perchlorates (Ventron Alfa Products) and sodium 2,4,6-trinitrobenzenesulfonate (Baker) were used without further purification. Methylene blue (certified quality, Aldrich) was recrystallized twice from ethanol/water. 1-Benzyl-1,4-dihydronicotanimide and 1-propyl-1,4-dihydronicotinamide were prepared according to the literature.[18] Methanol, acetonitrile, and chloroform used in the kinetic experiments were of analytical grade and distilled under nitrogen before use.

3-Carbamoyl-1-(1,10-phenanthrolin-2-ylmethyl)-pyridinium Chloride (2). To a solution of 200 mg (0.73 mmol) of 2-(aminomethyl)-1,10-phenanthroline·$CH_3COOH \cdot H_2O$[19] in 10 mL of methanol was added 240 mg (0.74 mmol) of 3-(aminocarbonyl)-1-(2,4-dinitrophenyl)pyridinium chloride[20] in 10 mL of methanol. The deeply red colored reaction mixture was stirred for 1.5 h at 60 °C and turned yellow. Addition of 80 mL of ether yielded a precipitate which was filtered off by suction and washed with 3 × 10-mL portions of acetonitrile. The yellow solid was suspended in 20 mL of acetonitrile and sonified for 10 min. The acetonitrile was decanted, and this procedure was repeated until

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the acetonitrile turned no longer yellow. Yield 210 mg (74%) of **2** as a white solid: mp 223–225 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.49 (s, 2 H), 7.87 (dd, 1 H, J = 4.5, 8.1 Hz), 8.08 (d, 1 H, J = 8.2 Hz), 8.12 (s, 2 H), 8.30 and 8.87 (br s, NH_2), 8.44 (dd, 1 H, J = 6.0, 8.0 Hz), 8.62 (br d, 1 H, J = 8.1 Hz), 8.72 (d, 1 H, J = 8.2 Hz), 9.12 (dd, 1 H, J = 2.0, 4.5 Hz), 9.17 (d, 1 H, J = 8.0 Hz), 9.55 (d, 1 H, J = 6.0 Hz), 9.95 (br s, 1 H). Anal. Calcd for $C_{19}H_{15}ClN_4O\cdot 2H_2O$: C, 58.99; H, 4.95. Found: C, 58.78; H, 4.85.

1,4-Dihydro-1-(1,10-phenanthrolin-2-ylmethyl)-3-pyridinecarboxamide (3). A 200-mg (0.52-mmol) sample of **2**·2H_2O was dissolved in a solution of 2 g of Na_2CO_3 in 25 mL of water. Sodium dithionite (0.5 g) was added in small portions during 10 min, and the pale yellow reaction mixture was stirred under nitrogen for 2 h. After extraction with freshly distilled chloroform, drying the chloroform layer over Na_2SO_4, and removal of the chloroform in vacuo at room temperature, 120 mg (73%) of **3** as an yellow-orange solid was obtained: mp 155–160 °C dec; ^{1}H NMR (CD_3CN, 300 MHz) δ 3.27 (m, 2 H), 4.89 (s, 2 H), 4.92 (dt, 1 H, J = 3.5, 8.0 Hz), 6.15 (dq, 1 H, J = 1.7, 8.0 Hz), 7.28 (d, 1 H, J = 1.7 Hz), 7.74 (s, 2 H), 7.86 (m, 2 H), 8.53 (dd, 1 H, J = 1.8, 8.2 Hz), 8.57 (d, 1 H, J = 8.2 Hz), 9.11 (dd, 1 H, J = 1.8, 4.3 Hz); ^{1}H NMR (CD_3CN plus 1 equiv of $Zn(ClO_4)_2\cdot 6H_2O$, 300 MHz) δ 5.25 (br s, 2 H), 6.60 (s, 2 H), 6.65 (br s, 1 H), 7.25 (br s, 1 H), 7.64 (br s, 1 H), 8.10–8.20 (m, 4 H), 8.75 (br m, 1 H), 8.92 (br m, 1 H), 9.27 (br s, 1 H).

1,4-Dihydro-1-(1,10-phenanthrolin-2-ylmethyl)-3-pyridinecarboxamide-4-*d* (3-4-*d*). The same procedure as for **3** has been employed using D_2O as the solvent. The ^{1}H NMR absorbance at δ 3.27 was in accordance with 50 (±2)% deuteration of the 4-position of the dihydronicotinamide ring.

***N*-(1,10-Phenanthrolin-2-ylmethyl)-3-pyridinecarboxamide (4).** To a suspension of 3.0 g (11 mmol) of 2-(aminomethyl)-1,10-phenanthroline·$CH_3COOH\cdot H_2O$[19] in 60 mL of $CHCl_3$ was added 6.0 g (33 mmol) of 3-pyridinecarbochloride and 10 mL of triethylamine. The reaction mixture was refluxed and was followed by TLC ($CHCl_3$–CH_3OH, 9:1) to completion. After 3 h the solvent was removed in vacuo, and 150 mL of water was added to the residue. The solution was neutralized with Na_2CO_3, and after 1 h of stirring the precipitate was filtered off and washed with water. The product was recrystallized from methanol–water, yielding 2.45 g (69%) of **4** as a white solid: mp 225–226 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.10 (br d, 2 H, J = 5 Hz), 7.30 (ddd, 1 H, J = 0.9, 4.8, 8.0 Hz), 7.69 (dd, 1 H, J = 4.5, 8.0 Hz), 7.75 (d, 1 H, J = 8.1 Hz), 7.79 (br s, 2 H), 8.15 (d, 1 H, J = 8.1 Hz), 8.25 (dd, 1 H, J = 1.8, 8.0 Hz), 8.31 (ddd, 1 H, J = 1.8, 2.8, 8.0 Hz), 8.68 (dd, 1 H, J = 1.8, 4.8 Hz), 9.10 (dd, 1 H, J = 1.8, 4.5 Hz), 9.28 (dd, 1 H, J = 0.9, 2.8 Hz). Anal. Calcd for $(C_{19}H_{14}N_4O)_2\cdot H_2O$: C, 70.57; H, 4.68; N, 17.33. Found: C, 70.76; H, 4.50; N, 17.19.

3-[[(1,10-Phenanthrolin-2-ylmethyl)amino]carbonyl]-1-(phenylmethyl)pyridinium Bromide (5). To 0.5 g (1.55 mmol) of **4** in 30 mL of dimethylformamide was added 0.29 g (2.0 mmol) of zinc bromide and 1 g (5.8 mmol) of benzylbromide. The mixture was stirred for 20 h at 45–50 °C. After cooling, ether was added and a pale yellow oil separated. The oil was washed with five 10-mL portions of ether by decantation. After addition of 25 mL of water the oil solidified, and after stirring for 1 h the crystalline solid was filtered off by suction. Recrystallization from CH_3OH–H_2O yielded 0.81 g (74%) of **5** as the zinc bromide salt: mp 180–185 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.09 (br s, 2 H), 6.02 (s, 2 H), 7.50–7.65 (m, 5 H), 8.01 (d, 1 H, J = 8.3 Hz), 8.12 (dd, 1 H, J = 4.4, 8.0 Hz), 8.21 (s, 2 H), 8.42 (dd, 1 H, J = 6.5, 8.0 Hz), 8.68 (d, 1 H, J = 8.3 Hz), 8.94 (br d, 1 H, J = 8.0 Hz), 9.20 (br d, 1 H, J = 8.0 Hz), 9.27 (br d, 1 H, J = 4.4 Hz), 9.39 (br d, 1 H, J = 6.5 Hz), 9.79 (br s, 1 H), 10.11 (br s, 1 H). Anal. Calcd for $C_{26}H_{22}Br_3N_4OZn$: C, 43.94; H, 3.17. Found: C, 44.11; H, 3.08.

1,4-Dihydro-*N*-(1,10-phenanthrolin-2-ylmethyl)-1-(phenylmethyl)-3-pyridinecarboxamide (6). In a nitrogen atmosphere, 300 mg (0.42 mmol) of **5**–$ZnBr_2$ was dissolved in a solution of 2.0 g of Na_2CO_3 in 50 mL of water. The solution became turbid due to precipitation of zinc carbonate. Sodium dithionite (0.5 g, 2.44 mmol) was added in small portions during 10 min, and the color of the reaction mixture turned to pale yellow. After an additional 15 min of stirring the mixture was extracted with freshly distilled dichloromethane. After the dichloromethane layer was dried with Na_2SO_4, the solvent was removed in vacuo at 20 °C in the dark. This yielded 125 mg (74%) of **6** as an unstable yellow solid which decomposed rapidly upon heating. Upon storage at −20 °C, approximately 20% decomposition had occurred after 24 h. Therefore, all kinetic runs were performed with freshly prepared **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.24 (m, 2 H), 4.27 (s, 2 H), 4.72 (dt, 1 H, J = 3.4, 7.8 Hz), 4.94 (s, 2 H), 5.70 (dq 1 H, J = 1.6, 7.8 Hz), 7.20–7.28 (m, 6 H), 7.64 (dd, 1 H, J = 4.5, 8.0 Hz), 7.70–7.82 (m, 3 H), 8.20 (d, 1 H, J = 7.8 Hz), 8.26 (dd, 1 H, J = 1.5, 8.0 Hz), 9.14 (dd, 1 H, J = 1.5, 4.3 Hz).

Methods. Absorbance spectra and kinetic measurements were run on a Beckman DU-7 spectrophotometer with a thermostated cell compartment and kinetic device or on an HP 8452A diode array spectrophotometer. The temperature was controlled at 25 ± 0.1 °C. Binding constants of zinc ion to **2** and **3** in methanol were determined by quantitative measurements of the absorbance changes at 275 nm of 3×10^{-5} M solutions of **2** and **3** upon variation of the zinc perchlorate concentration. The ionic strength of the solution was kept constant (0.1 M) with sodium perchlorate. Rate constants were determined at least in triplicate.

Transhydrogenation reactions of **2** and **2**–Zn^{2+} with *n*-PrNAH were measured in methanol at 25 °C under pseudo-first-order conditions. Therefore, overlay spectra were recorded in the 300–420-nm range of sample solutions containing 1.0×10^{-3} M **2** and 1.1×10^{-4} M *n*-PrNAH in the absence and presence of 0.1 M zinc perchlorate, respectively. A logarithmic plot of the decrease of absorbance at 365 nm, ln $(A_t - A_\infty)$, was linear with time with slope $k_2/[2]$.

The oxidation rates of **3**, **3**–Zn^{2+}, **6**, **6**–Zn^{2+}, and BNAH by MB^+ and by TNBS were determined by following the decrease in absorbance of the dihydronicotinamide group in the 350–365-nm range. Sample solutions for MB^+ reactions were made by mixing 1 mL of 1.35×10^{-5} M aqueous MB^+ with 1 mL of 2.65×10^{-4} M **3**, **6**, or BNAH in acetonitrile. Sample solutions for TNBS reactions were made by mixing 1 mL of 2.65×10^{-4} M solutions of **3**, **6**, and BNAH in acetonitrile/water (1:5 vv) with 1 mL of a 10^{-2} M solution of TNBS in water. For reactions with **3**–Zn^{2+} and **6**–Zn^{2+} an extra 10 μL of 8.4×10^{-2} M zinc perchlorate in acetonitrile was added to the sample solution. Plots of ln $(A_t - A_\infty)$ vs time showed good pseudo-first-order dependency. In the reaction of the dihydronicotinamides with MB^+ the reduced MB^+ is rapidly reoxidized by molecular oxygen keeping the concentration MB^+ constant during the reaction.[12]

For reactions of the model compounds with PyCHO, stock solutions of **3** and **6** were made in acetonitrile. A stock solution of 2.65×10^{-4} M of **3** was stable in the dark for several days. Before each experiment, the quality was checked by measurement of the absorbance at 350 nm (A = 1.266 in a 1-cm cuvette), and a fresh stock solution was prepared when the absorbance was decreased by more than 5%. Solutions of **6** in acetonitrile were less stable and decompose with half-lives of ca. 2 days. Therefore, freshly prepared solutions of **6** (2.65×10^{-4} M) were used throughout the experiments, and, where necessary, rate constants were corrected for the decomposition rate. Stock solutions of PyCHO were made up in chloroform since PyCHO decomposes slowly in acetonitrile. Stock solutions of the metal salts were made up in acetonitrile. In the samples containing equimolar concentrations of PyCHO, metal salt, and **3**, 5 μL of 8.4×10^{-2} M metal perchlorate solution was injected into a 1-cm reaction cuvette containing 1.9 mL of stock solution of **3** (2.65×10^{-4} M) and 100 μL of 5.04×10^{-3} M PyCHO so that the ultimate concentration of the reactants was 2.52×10^{-4} M. For sample solutions of **6**, an extra 5 μL of metal perchlorate solution was added.

The reaction was monitored at 350 nm (for **3**) or 365 nm (for **6**), and second-order rate constants were evaluated from the equation $C_0^{-1} - C_t^{-1} = -k_2 t$, where C_0 and C_t represent the concentrations of **3**–Zn^{2+} or **6**–Zn^{2+} calculated from the molar extinction and the measured absorbance at $t = 0$ and $t = t$, respectively. Both the presence of 5% of $CHCl_3$ and metal ion promotes decomposition of **3**. For example, in 2.52×10^{-4} M solution of **3**, equimolar amounts of Zn^{2+} and Cd^{2+} induce a decomposition of ca. 5% after 1 h, Mg^{2+} of ca. 15%, and Co^{2+} of ca. 25%. However, in reaction of **3** with PyCHO this decomposition only gives a minor contribution to the observed reaction rate (the maximum is 10% for Co^{2+}), and, where necessary, rate constants have been corrected for it. Exposure of the sample solution to light accelerates the decomposition considerably, and

therefore all kinetic measurements have been performed by discontinueous exposure of the sample to the light beam of the spectrophotometer.

Reactions with variable concentrations of PyCHO and metal perchlorate were performed under pseudo-first-order conditions, and k_{obsd} values were calculated according to the method of Guggenheim using the Beckman kinetic programme. The time taken between the runs was always longer than 2 half-lives. Good pseudo-first-order plots were obtained for reactions where sufficient metal ion was present in order to prevent loss of the phenanthroline-chelated metal ion to excess of PyCHO. For those reactions where PyCHO was in large excess over metal ion, however, the observed reaction rate rapidly decreases and initial reaction rates have been calculated.

Product Analysis. A solution of equivalent amounts (0.5 mmol) of 2-pyridinecarboxaldehyde, **3**, and zinc perchlorate in 25 mL of acetonitrile was kept under a nitrogen atmosphere in the dark for one night. The solvent was evaporated in vacuo, and 5 mL of an aqueous solution of 1 mmol of EDTA was added, followed by extraction of the mixture with 3 × 20 mL of dichloromethane. The organic layer was dried on Na_2SO_4, and after filtration the solution was evaporated, yielding 47 mg of a pale yellow oil. A sample of this residue was subjected to GC–MS analysis and identified as 2-pyridinemethanol (92%) and 2-pyridinecarboxaldehyde (8%). Column chromatography on silica ($CHCl_3$–CH_3OH, 95:5) yielded 37 mg (69%) of 2-pyridinemethanol. The ^1H NMR spectrum of this product was identical with that of an authentic sample.

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Notes

Ligand-Controlled α-Regioselectivity in Palladium-Catalyzed Arylation of Butyl Vinyl Ether

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The palladium-catalyzed arylation of olefins (Heck reaction) is an extremely useful process for carbon–carbon bond formation;[1,2] unfortunately the use of acyclic enol ethers in this reaction is limited by poor α/β-regioselectivity (Figure 1). Preferential β-attack was observed with aromatic substrates bearing electron-withdrawing groups and when chloride or bromide anions are present in the oxidative addition intermediate.[3] On the other hand, high selectivity for the α position in acyclic systems has so far been observed only in a few cases[4a,b] and in reaction between vinyl triflates and enol ethers.[4c]

In connection with our previous work on the use of DPPP ligands in reactions of aryl triflates,[5] we investigated the $Pd(AcO)_2$-DPPP system in the reaction between aryl triflates and enol ethers.

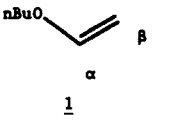

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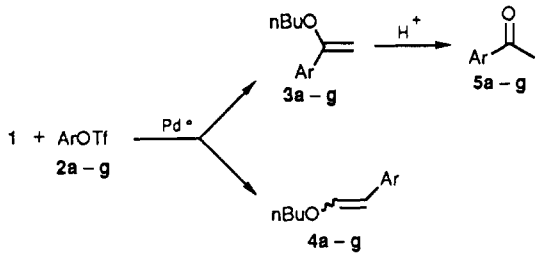
Figure 1.

Scheme I[a]



[a] **a**, 1-naphthyl; **b**, *p*-NO_2-phenyl; **c**, *p*-CN-phenyl; **d**, *p*-CH_3CO-phenyl; **e**, phenyl; **f**, *p*-CH_3-phenyl; **g**, *p*-CH_3O-phenyl.

Table I. Palladium-Catalyzed Arylation of Butyl Vinyl Ether (1) with Naphthyl Triflate (2a)[a]

entry	solvent	ligand (L/Pd[b])	T (°C)	t (h)	3a/4a[c]	product (yield, %[d])
1	DMF	none	100	24[e]	54/46	**4a** (3)[f] + **5a** (4)
2	DMF	PPh_3 (2)	100	1.5	63/37	**4a** (32)[g] + **5a** (58)[h]
3	DMF	DPPP (1.1)	80	0.5	100/0	**5a**[h] (97)
4	DMF	DPPP (1.1)	60	1	100/0	**5a**[h] (91)
5	DMF	DPPP (1.1)	40	12.5	100/0	**5a**[h] (94)
6	dioxane	DPPP (1.1)	80	1.5	100/0	**5a**[h] (89)
7	toluene	DPPP (1.1)	80	2	100/0	**5a**[h] (95)

[a] The naphthyl triflate (3.6 mmol), butyl vinyl ether (18.1 mmol), triethylamine (7.24 mmol), $Pd(OAc)_2$ (0.09 mmol), and ligand were reacted in 10 mL of DMF. [b] Molar ratio between ligand and $Pd(AcO)_2$. [c] Determined by GLC of the crude products before acidic treatment. [d] Isolated yields. [e] Conversion (7%) and yields determined by GLC. [f] **4a** was present as a 71/29 *E*/*Z* mixture, determined by GLC. [g] **4a** was isolated as an 80/20 *E*/*Z* mixture, determined by GLC and ^1H NMR. [h] **5a**: bp 160–162 °C (11 mmHg), lit.[8] bp 167–170 °C (13 mmHg).

Results and Discussion

The catalyst generated in situ from 1,3-bis(diphenylphosphino)propane (DPPP) and $Pd(AcO)_2$ promotes the

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(2) For Heck reaction on aryl perfluoroalkanesulfonate, see: (a) Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171. (b) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386. (c) Chen, Q.-Y.; He, Y.-B. *Synthesis* **1988**, 896.

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