with assignments for 7). Anal. Calcd for $C_{27}H_{29}ClN_2S_2O_3$: C, 61.29; H, 5.52; Cl, 6.70; N, 5.30; S, 12.12. Found: C, 61.30; H, 5.57; Cl, 6.65; N, 5.23; S, 12.10.

From O-Silylated Hemithioacetal 10. The O-silylated hemithioacetal reaction mixture as described above (ca. 34 mmol of 10) was filtered, and the resulting CH_2Cl_2 solution was cooled to -50 °C. Methyl 3-mercaptopropionate (4.33 mL, 39.1 mmol) was added followed by dropwise addition of BF_3·Et_2O (21.0 mL, 170 mmol) with mechanical stirring at <-45 °C. The reaction mixture was stirred at -50 °C for 16 h and then was quenched by addition to a stirred solution of 15% aqueous Na_2CO_3 (200 mL). Additional CH_2Cl_2 (100 mL) was added, and the resulting organic layer was separated, washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo at ≤30 °C to give the crude product as a 8:1:1 mixture of 7:8:6. Purification as described above gave ester-amide 7 (10.9 g, 61%).

L-660,711 (1). Ester-amide 7 (746 g, 1.41 mol) was dissolved in warm THF (8.8 L) and cooled to -3 °C. A solution of 1.00 N aqueous LiOH (1.48 L, 1.48 mol) was added dropwise with mechanical stirring over ca. 1.2 h at ≤0 °C. After an additional 2 h at -1 to 1 °C, extra 1.00 N aqueous LiOH (70 mL, 0.070 mol) was added. After a total reaction time of 4.5 h at -3 to 2 °C, water (12 L; precooled to 5 °C) was added and the THF was removed in vacuo at ≤20 °C. The resulting aqueous concentrate was extracted with EtOAc (2 × 4.5 L) and transferred to a round-bottomed flask equipped with a mechanical stirrer. 2-Propanol (13 L) was added, and the pH was adjusted to 6.0 with concentrated HCl. Seed crystals of 1 (ca. 7 g) were added, and the pH was adjusted to 3.5 with 2 N aqueous HCl. After being stirred for 16 h at ambient temperature, the resulting product was filtered, rinsed with 2-propanol (7 L), and dried in vacuo at 50 °C overnight to give crystalline 1 (639 g, 88%; ≥97% pure by HPLC). An analytical sample was prepared by recrystallization from 2-butanone: mp 161.5-163 °C; ^{1}H NMR (DMSO-d_6) δ 2.5-3.4 (overalpping multiplets, 4 CH_2), 2.79, 2.89 (2 s, $N(CH_3)_2$), 5.32 (s, Ar-CH), 7.44 (m, 5'-H, 6'-H), 7.47 (d, J = 16.5, 3'-CH=), 7.59 (dd, J = 8.7, 2.3 Hz, 6-H), 7.67 (m, 4'-H), 7.80 (b s, 2'-H), 7.87 (d, J = 16.5 Hz, 2-CH=), 7.95 (d, J = 8.6 Hz, 3-H), 8.00, 8.03 (overlapping doublets, 5-H, 8-H), 8.40 (d, J = 8.6 Hz, j-H), 12.3 (broad, CO_2H). Anal. Calcd for $C_{26}H_{27}ClN_2S_2O_3$: C, 60.63; H, 5.28; Cl, 6.88; N, 5.44. Found: C, 60.68; H, 5.36; Cl, 6.98; N, 5.35.

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Registry No. 1, 120663-36-7; 2, 120578-03-2; 3, 4965-33-7; 4, 626-19-7; 5, 120578-04-3; 6, 120385-96-8; 7, 120663-37-8; 8, 120578-05-4; 10, 120578-06-5; methyl 3-mercaptopropionate, 2935-90-2; *N,N*-dimethylacrylamide, 2680-03-7; *N,N*-dimethyl-3-mercaptopropionamide, 5458-01-5; thiolacetic acid, 507-09-5.

Reactivity of Biologically Important Reduced Pyridines. 4. Effect of Substitution on Ferricyanide-Mediated Oxidation Rates of Various 1,4-Dihydropyridines†

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The effect of substitution on the rate of ferricyanide-mediated oxidation of various dihydropyridines was examined. 1-Alkyl-, 1-aralkyl-, 1-aryl-, and 6-substituted 1-methyl-1,4-dihydronicotinamides, 3-substituted 1-methyl-1,4-dihydropyridines, and quinoline and isoquinoline derivatives were subjected to ferricyanide oxidation. Increasing the *n*-alkyl chain of 1-methyl-1,4-dihydronicotinamide acted to slowly decrease the rate of oxidation. The 1-cyclopropyl-1,4-dihydronicotinamide was shown to be unusually stable compared to the 1-isopropyl derivative due presumably to the electron-withdrawing nature of the π-like substituent. 1-(4-Substituted phenyl)-1,4-dihydronicotinamides over the range of *p*-NO_2 (σ = 0.778) to *p*-$N(CH_3)_2$ (σ = 0.83) generated a linear Hammett plot (r = 0.9994) with a reaction constant of ρ = 2.76, consistent with an initial electron removal in the rate-determining step of oxidation. When substitutions at the 3-position are considered, the rank order of stability was CHO > CN > $COCH_3$ > $COOCH_3$ > $CONH_2$ > CONHR > $CONR_2$ and is related to the electron-withdrawing potency of the moiety. Finally the 1-methyl-1,4-dihydro-3-quinolinecarboxamide was found to be much more stable than the 2-methyl-1,2-dihydro-4-isoquinolinecarboxamide.

Introduction

The occurrence of dihydropyridine partial structures in biologically important coenzymes such as NADH and NADPH has made these compounds an appealing subject for study.[1] Of particular importance is the mechanism of oxidation of substituted dihydropyridines. The classical work of Abeles and Westheimer suggested that the oxidation of various dihydropyridines by thiobenzophenones was mediated by concerted hydride transfer.[2] Later, discrepancies between kinetic isotope effects and product isotope compositions indicated that intermediates existed on the reaction coordinate for this process.[3] Postulated intermediates included radical cations which can be formed

† Part 3 of this series: Bodor, N.; Brewster, M.; Kaminski, J. Energetics and Mechanism of the Hydride Transfer between 1-Methyl-1,4-dihydronicotinamide and the 1-Methylnicotinamide Cation *J. Molecular Structure* (Theochem), in press.

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⊥ On leave from the Technical University of Budapest, Budapest, Hungary.

∥ On leave from the Institute of Drug Research, Budapest, Hungary.

On leave from the University of Assiut, Assiut, Egypt.

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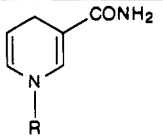
Table I. Second-Order Rate Constants for Ferricyanide-Mediated Oxidation and Lipophilicity Information for a Series of 1-Alkylated 1,4-Dihydronicotinamides



(R)	compd no.	k_0 (s^{-1} M^{-1}) ± SE[a]	R_m[b]	carbon[c] number
methyl	1	59.73 ± 0.97	0.79	1
ethyl	2	50.03 ± 1.08	1.21	2
propyl	3	38.70 ± 2.14	1.70	3
butyl	4	37.28 ± 1.94	2.29	4
pentyl	5	28.44 ± 0.54	3.00	5
hexyl	6	22.46 ± 0.16	3.32	6
heptyl	7	25.13 ± 1.24	3.95	7
octyl	8	22.98 ± 0.49	4.50	8
nonyl	9	20.43 ± 0.92	5.15	9
decyl	10	18.68 ± 1.53	5.41	10
isopropyl	11	40.43 ± 0.97		3
tert-butyl	12	29.46 ± 1.51		4
1-adamantyl	13	29.31 ± 1.13		10
cyclopropyl	14	4.40 ± 0.07		3
methylcyclopropyl	15	27.31 ± 1.13		4

[a] k_0 ± standard error of the slope (SE). [b] R_m values for 1-alkyl-1,4-dihydronicotinamides. [c] Number of carbons associated with the 1-substituent.

by an initial electron removal from the dihydropyridines. This unstable species could then degrade to the quaternary salt via hydrogen atom loss or via sequential proton, electron abstractions.[4] The finding that many of the discrepancies which prompted the suggestion of intermediates could be explained by quantum mechanical events and productive and unproductive side reactions supported the notion that hydride transfer was synchronous.[1,5] Taken as a whole, the data collected over the years on the oxidation of dihydropyridines suggest that reaction conditions often determine the mechanism of oxidation. In the presence of potent one-electron oxidants such as the ferricyanide ion or ferricenium cation, the reaction proceeds through an initial electron removal followed by proton loss and a subsequent non-rate-determining electron ionization.[6] In the presence of hydride acceptors with poor one-electron oxidation potentials, concerted hydride transfer appears to occur. Appropriate hydride acceptors include various substituted pyridinium, quinolinium, and acridinium salts and substituted phenones.

The reaction of potassium ferricyanide with dihydropyridines has been extensively studied by Bruice and his associates.[5] This oxidation is associated with a small but significant kinetic isotope effect and is subject to inhibition upon addition of ferrocyanide ions. These observations indicate that ferricyanide-mediated oxidation of dihydropyridines is not a pure one-electron process and that the rate of this reaction is influenced to some degree by deprotonation, i.e., the second step in the oxidation. Importantly, when a strong base is available in the oxidation media, deprotonation is rapid and the rate of oxidation is primarily associated with the initial electron loss. It is only when general bases are present in the reaction sequence that rate contributions from deprotonation become significant. Ferricyanide-mediated oxidation can therefore be a useful means of looking at compound reactivity associated with one-electron oxidation although it is not a measure purely of this phenomenon.

We were interested in the effect of structure on the rates of one-electron oxidation of dihydropyridines as measured by ferricyanide-mediated reaction since few studies examining large numbers of compounds have appeared in the literature. Information generated by this examination is applicable to the nature of hydride transfer since the rates of electron loss and the rates of hydride loss for various dihydropyridines have been shown to be highly correlated.[5] In addition, a method allowing for in vitro determination of oxidative stability could be useful in predicting the effectiveness of various pharmacologically active agents which require oxidation for either their inactivation (nifedipine-type calcium channel blockers)[7] or their activation (brain-targeting chemical delivery systems).[8] In the present paper, the effect of substitution on dihydropyridines at the 1,3,5- and/or 6-position is examined in the context of potassium ferricyanide-mediated oxidation.

Results and Discussions

Chemistry. Compounds used in these studies were prepared by one of two routes. 1-Alkylated or aralkylated nicotinamides or pyridinium salts containing various 3-substituents were prepared by quaternization of the appropriate substituted pyridine with an appropriate alkyl halide. The resulting salts were then reduced in basic aqueous sodium dithionite.[9] For 1-phenyl derivatives as well as the 1-*tert*-butyl, 1-adamantyl, and cyclopropyl compounds, 1-(2,4-dinitrophenyl)nicotinamide chloride,[10]

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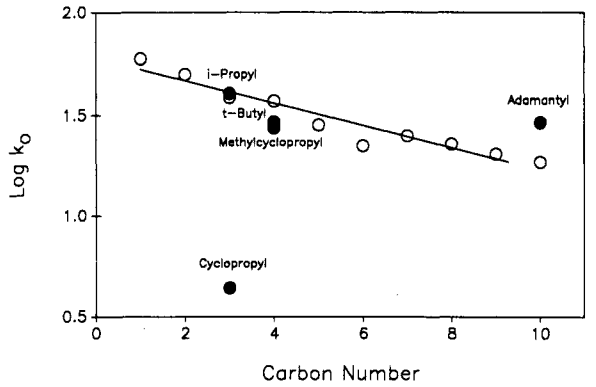


Figure 1. Effect of 1-alkyl substitution on the rate of ferricyanide-mediated oxidation of 1,4-dihydronicotinamide. Open circles represent the methyl to decyl homologous series. Filled circles represent branched or cycloalkyl derivatives. In this study correlation between log k_0 and carbon number for the homologous series was significant (r = 0.963).

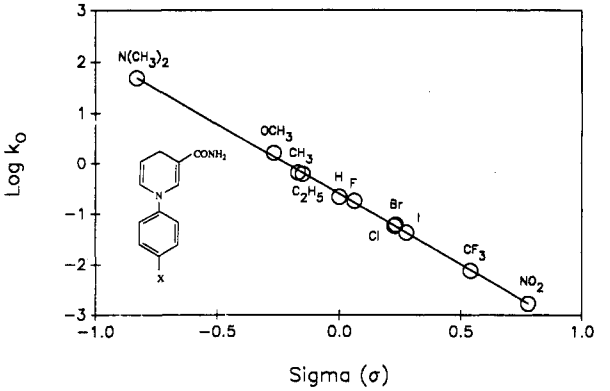


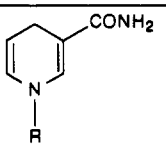
Figure 2. Hammett σ–ρ analysis for a series of 1-(4-substituted phenyl)-1,4-dihydronicotinamides and their rates of ferricyanide-mediated oxidation. In this study the correlation was significant (r = 0.9994) and the reaction constant (ρ) was found to be −2.76.

a so-called Zincke salt, was reacted with either the appropriate aniline or the appropriate primary amine, giving rise to the pyridinium salts via an ANRORC mechanism.[11] In the case of 1-phenyl moieties which were substituted in the para position with highly electron withdrawing groups such as trifluoromethyl or nitro, the addition of catalytic amounts of pyridine to the reaction mixture was essential.[12] The obtained pyridinium salts were then reduced with sodium dithionite in basic aqueous media.[13] Substituted amides were obtained by reacting nicotinoyl chloride or nicotinic anhydride with the appropriate primary or secondary amine. 3-Quinolinecarboxamide and 4-isoquinolinecarboxamide were prepared by literature procedures,[14] methylated with methyl iodide, and reduced with sodium dithionite.

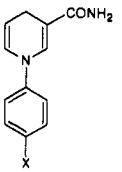
1-Alkyl-1,4-dihydronicotinamides. Table I summarizes the second-order rate constants obtained for ferricyanide-mediated oxidation of a series of 1-alkyl-, branched alkyl, and cycloalkyl-1,4-dihydronicotinamides. In addition, lipophilicity information (R_m)[15] is given for a homologous series of 1-*n*-alkyl derivatives. There is a high degree of correlation between lipophilicity and the number of carbons in the group substituted at the 1-position (r = 0.998) as expected. There is also significant correlation between each of these parameters and the log k_0 for oxidation. A plot of carbon number and log k_0 is presented in Figure 1 (r = 0.963). The decrease in rate of oxidation with carbon length has several potential causes including steric crowding and a lower degree of solvation of more lipophilic derivatives.

Branching of the 1-alkyl group has little effect on reactivity. As illustrated in Figure 1, the 1-isopropyl and 1-*n*-propyl compounds are of similar reactivities as are the *n*-butyl and *tert*-butyl derivatives. The 1-adamantyl substituent is slightly more reactive than the 1-decyl derivative, which may relate to its more compact nature. The 1-cyclopropyl-1,4-dihydronicotinamide is almost 10-fold more stable than either the isopropyl or the *n*-propyl compounds. This effect is no doubt related to the electron-withdrawing nature of the strained, π-like cyclopropyl group.[16] The high p-character of the ring bonds imparts high s-character to the N–C bond, allowing for higher electron delocalization from the dienamine system. If a methylene insulator is placed between the cyclopropyl and dihydronicotinamide fragments, the stabilizing effects of the cyclopropyl moiety are negated.

Table II. Second-Order Rate Constants for Ferricyanide-Mediated Oxidation for a Series of 1-Aryl- or 1-Aralkyl-1,4-dihydronicotinamides



(R)	compd no.	k_0 (s^{-1} M^{-1}) ± SE
phenyl	16	0.22 ± 0.001
benzyl	17	2.28 ± 0.06
phenethyl	18	11.84 ± 0.65
phenpropyl	19	20.26 ± 0.52
propargyl	20	0.52 ± 0.015



(X)		
$N(CH_3)_2$	21	48.13 ± 4.09
OCH_3	22	1.61 ± 0.03
CH_3	23	(6.55 ± 0.41) × 10^{-1}
C_2H_5	24	(6.15 ± 0.09) × 10^{-1}
F	25	(1.80 ± 0.09) × 10^{-1}
Cl	26	(5.80 ± 0.23) × 10^{-2}
Br	27	(6.10 ± 0.31) × 10^{-2}
I	28	(4.26 ± 0.17) × 10^{-2}
CF_3	29	(7.60 ± 0.46) × 10^{-3}
NO_2	30	(1.71 ± 0.01) × 10^{-3}

1-Aryl and -Aralkyl Substitution (Table II). Placement of a phenyl ring at the 1-position of 1,4-dihydronicotinamide (**16**) has a strong stabilizing effect, decreasing the rate of oxidation approximately 270-fold relative to 1. The phenyl group represents an excellent sink for the dienamine electrons and acts to tremendously lower the energy of the highest occupied molecular orbital

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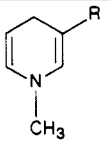
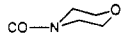
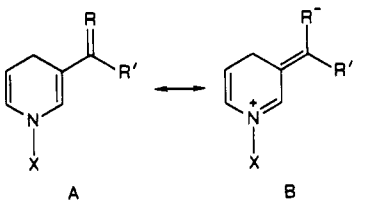
Table III. Second-Order Rate Constants for Ferricyanide-Mediated Oxidation for a Series of 3-Substituted 1-Methyl-1,4-dihydropyridines



(R)	compd no.	k_0 (s^{-1} M^{-1}) ± SE
CHO	31	<0.05
CN	32	0.21 ± 0.002
$COCH_3$	33	1.18 ± 0.04
CO_2CH_3	34	3.82 ± 0.07
$CO_2C_2H_3$	35	4.31 ± 0.19
$CONH_2$	1	59.73 ± 0.97
$CONHC_2H_5$	36	133.3 ± 1.17
$CONHC_6H_5$	37	37.2 ± 0.68
$CON(C_2H_5)_2$	38	3065.0 ± 142.0
$CON(C_6H_5)_2$	39	40.86 ± 1.83
$CON(C_2H_5)(C_6H_5)$	40	396.7 ± 40.6
$CONHCH_2C_6H_5$	41	50.11 ± 0.55
$CONHCH_2CH_2C_6H_5$	42	82.3 ± 2.09
$CON(CH_2C_6H_5)(t\text{-}C_4H_9)$	43	1023.0 ± 242.0
	44	748.8 ± 84.8

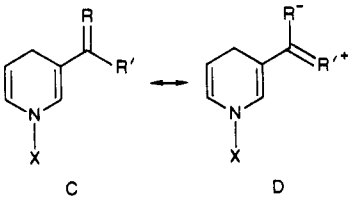
(HOMO). Again, insulation of the phenyl and dihydropyridine groups dampens this stabilization but not as dramatically as in the 1-cyclopropyl case. A propylene group separating the two fragments is required before the reactivity of the system approaches that of the 1-alkyl derivatives. A 1-propargyl group also stabilizes the 1,4-dihydronicotinamide, and the degree of stabilization is similar to that produced by a 1-phenyl substitution. The effect of 4-substitution on the phenyl moiety of **16** is presented in Figure 2. The Hammett σ–ρ plot generated is highly linear (r = 0.9994) over the entire range of oxidation rates (over 4 orders of magnitude). The reaction constant obtained from this study was ρ = −2.76. The negative slope is consistent with an initial, rate-determining electron removal generating a radical cation.[17] It is not consistent with a rate-determining proton removal from the radical cation as one would expect electron-withdrawing substituents to accelerate this process. The *p*-nitro group would also be expected to merostabilize[18] the neutral radical formed to a greater extent than the radical cation. The reaction constant obtained in this study is similar to that calculated for other reactions where the electron density on nitrogen is important for determining reactivity. The reaction of benzoyl chloride with para substituted anilines for example produced a ρ = −2.78.[19] These data are consistent with the interpretation that the transition state in the oxidation involves the formation of a positive charge on the heterocyclic nitrogen.

3-Substituted 1-Methyl-1,4-dihydropyridines. The effect of 3-substitution on the rate of oxidation of 1-methyl-1,4-dihydropyridines is summarized in Table III. The general order of reactivity obtained from this study was found to be: CHO < CN < $COCH_3$ < $COOCH_3$ < $CONH_2$ < CONHR < $CONHR_2$. The rationale for this rank order is related to the interaction of the 3-substituent with the dienamine structure. Canonical forms such as those given below will contribute to dihydropyridine stabilization by providing for greater electronic delocalization and lower HOMO energies:



A B

On the other hand, canonical structures such as C and D will tend to decrease delocalization and increase the energy of the HOMO. Thus carboxaldehydes are more stable than carboxylic acid esters, which are in turn more stable than carboxamides.[2]



C D

N′-Substitution of carboxamides will generally have a destabilizing effect by favoring structure D, but the nature of the substituent may attenuate the effect. The *N*′-ethyl amide is a little more than twice as reactive as the unsubstituted compound **1**, while the *N*′,*N*′-diethyl derivative is more than 50 times more reactive. Replacement of one of the ethyl groups with a phenyl moiety provides for a compound which is only 6.5-fold more reactive than **1**, while the *N*′,*N*′-diphenyl amide is slightly more stable than **1**. The effect of the phenyl groups in this case is partially inductive since steric restriction would prevent both phenyl groups from being planar with respect to the amide function at the same time. The *N*′-phenyl derivative is approximately 1.5-fold less reactive than **1**, and in this case there are few constraints on planarity. As in previous cases, placement of an sp^3 insulator between the phenyl and amide moieties acts to increase reactivity. Interestingly, this effect is approximately 100-times weaker in the case of the amide manipulation than N-1 substitution (Figure 3), which is presumably due to the indirect stabilizing interaction of the phenylamides. Such effect may be mediated by the lowest unoccupied molecular orbital (LUMO), whereas the 1-substituent interacts directly with the HOMO.

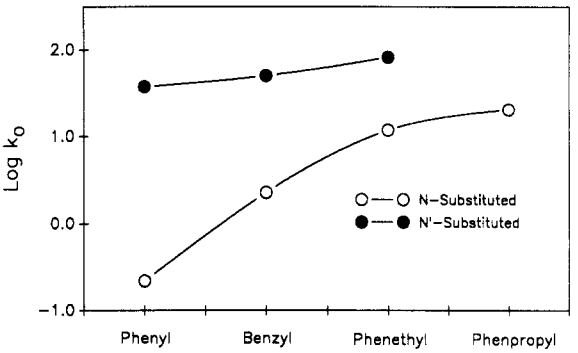


Figure 3. Effect of insulating a phenyl group at either the N-position or at the N′-position of a primary 3-carboxamide.

Other Derivatives. Placement of a methyl group in the 6-position of **1** has a destabilizing effect on the compound toward oxidation. This effect is related to the electron-denoting capabilities of the methyl function relative to hydrogen. Interestingly, the 6-chloro group has

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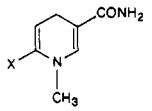
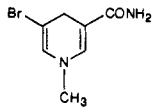
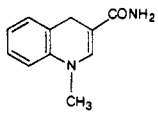
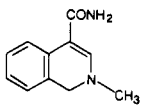
Table IV. Second-Order Rate Constants for Ferricyanide-Mediated Oxidation for a Series of Substituted 1,4-Dihydronicotinamides

compd	no.	k_0 (s^{-1} M^{-1}) ± SE
		
(X)		
CH_3	45	339.0 ± 19.0
Cl	46	41.2 ± 2.85
	47	0.33 ± 0.091
	48	0.096 ± 0.003
	49	15.76 ± 0.68

only a modest effect on reactivity (Table IV). If, however, a halogen is placed at the C-5 position, a significant stabilization is realized. The effect of annulation of a benzene ring at either the 5,6-position of **1** giving rise to 1-methyl-1,4-dihydro-3-quinolinecarboxamide or at the 4,5-position to give 2-methyl-1,2-dihydro-4-isoquinolinecarboxamide was also investigated (Table IV). The quinoline derivative is more than 600-fold more stable than **1** while the isoquinoline derivative is only 4-fold more stable. The interaction of the heterocyclic nitrogen with the benzene ring clearly facilitates electron delocalization in the quinoline case. The effect is more indirect in the 1,2-dihydroisoquinoline case.

Discussion

The use of potassium ferricyanide oxidation to study the effects of substitution on dihydropyridines was shown to be useful. As illustrated by the degrees of stabilization obtained by 1-cyclopropyl, 1-phenyl, and 1-aralkyl substitution, this method can detect subtle difference in electronic structure. Conversely, the method is insensitive to the effects of steric bulk as observed in the cases of 1-*tert*-butyl, 1-(1-adamantyl), and 6-methyl substitution. A study of a series of 1-(4-substituted phenyl)-1,4-dihydronicotinamides confirmed that the rate-determining step of the oxidation involved accumulation of a negative charge on the N-1 position consistent with an initial electron and inconsistent with a rate-determining proton loss. In addition, the highly linear Hammett $\sigma-\rho$ plot obtained suggest that a similar oxidative mechanism operates for all of these dihydronicotinamide (from *p*-nitro ($\log k_0 = -2.76$) to *p*-dimethylamino ($\log k_0 = 1.67$)).

The effect of various substitutions on the dihydropyridine nucleus are similar to those observed for hydride transfer and for acid-catalyzed degradation[2,5,17] (via the 6-hydroxytetrahydropyridines). The similarity of electron loss and hydride loss has been pointed out by Bruice and is reasonable since in both cases a positive charge is developed in the transition state.[5] Finally, the reactivity differences between 1,4-dihydroquinolines and 1,2-dihydroisoquinolines were described.

The use of ferricyanide-mediated oxidation to assay dihydropyridine stability has several practical applications including prediction of the pharmacological potency of various nifedipine-like Hansch esters[7] as well as dihydropyridine containing brain-targeting drug delivery systems.[8]

Experimental Section

Materials. Elemental analysis of compounds synthesized were performed by Atlantic Microlabs, Atlanta, GA. Melting points were determined with a Hoover-Thomas melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM 360 spectrometer. Samples were dissolved in an appropriate deuterated solvent, and chemical shifts (δ) were reported relative to an internal standard (tetramethylsilane, TMS). Ultraviolet (UV) spectroscopy was performed on a Hewlett-Packard 8451A diode array spectrophotometer. For kinetic analysis, the spectrophotometer was used in conjunction with an HP85 microprocessor. High-performance liquid chromatography (HPLC) was performed on a system consisting of a Perkin-Elmer Series 4 pump, a Kratos Spectroflow 757 variable-wavelength detector, a Perkin-Elmer ISS-100 integrator. All chemicals used were of reagent grade and obtained from either Aldrich Chemical Co. or Sigma Chemical Co. In the following section, general methods of preparation are given.

Compounds **1–11, 15, 17–20, 31–35, 38,** and **45–47** were prepared with the appropriate substituted pyridine and alkyl halide followed by reduction with sodium dithionite. Specifically, to 1 mmol of nicotinamide (or other substituted pyridines) in 50 mL of acetone was added 1.1 mol of an appropriate alkyl halide. The mixture was heated at gentle reflux for several hours. The mixture was cooled at which point the precipitated product was removed by filtration. If precipitation did not occur, the acetone was removed and the residue was recrystallized, usually from methanol–ethyl ether. The quaternary salt (10 mmol) was then dissolved in cold degassed water, and 50 mmol of $NaHCO_3$ was added, followed by 30 mmol of $Na_2S_2O_4$. The reaction mixture stirred under a stream of nitrogen for several hours at which time the aqueous phase was partitioned against several aliquots of CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, and reduced in volume. The residue was then reconstituted with CH_2Cl_2 and chromatographed on neutral alumina. The appropriate fractions were then combined, and the solvent was removed under reduced pressure, yielding (usually) an oil or yellow foam. Modifications to this procedure generally involved the solvent used in the quaternization (others found to be useful included acetonitrile, nitromethane, methanol, and dimethylformamide) and in the duration of the reduction step. For 1-alkyl groups that were hindered (**12–14**) and for 1-aryl derivatives **16,21–30** a different procedure was used. In these cases, 1 mmol of the appropriate aniline or primary amine dissolved in dry methanol was added to a solution of 1 mmol of 1-(2,4-dinitrophenyl)nicotinamide chloride[10] in 100 mL of methanol. The resulting red solution was then heated gently overnight or until the red color faded to yellow, indicating the formation of 2,4-dinitroaniline. The solution was cooled, and the precipitated side product was removed by filtration. The filtrate was then evaporated in vacuo, and the residue was dissolved in 100 mL of H_2O. The aqueous phase was then exhaustively washed with ethyl ether. The water layer was then evaporated under reduced pressure to give a crude product, which was recrystallized from methanol–ether. Reduction of the pyridinium salt is as described previously. In this procedure some changes were necessary for para substituted phenyl derivatives containing electron-withdrawing groups (compounds **29** and **30**). In these instances, it was necessary to add a catalytic amount (0.25 mL) of dry pyridine to the reaction mixture to facilitate quaternary salt formation. In addition, longer reduction times were required for compounds **29** and **30**. Four additional compounds were prepared for this study but could not be used since they were either photolytically unstable (1-(4-cyanophenyl)-, 1-(4-carbonylamino)phenyl)-, and 1-(4-acetylphenyl)-1,4-dihydronicotinamide) or were insoluble in the reaction media (1-(4-phenoxyphenyl)-1,4-dihydronicotinamide).

For the substituted amides (compounds **36, 37, 39–44**), 10 mmol of an appropriate primary or secondary amine in pyridine was slowly added to a solution of nicotinoyl chloride hydrochloride in 100 mL of pyridine. The solution was stirred at 50 °C for 2 h, at which time the system was cooled. The pyridine was removed under reduced pressure, and the residue was taken up in CH_2Cl_2 and washed with aqueous $NaHCO_3$. The organic layers were then dried and removed in vacuo to yield the crude amide, which was

then recrystallized (aqueous methanol, etc.). Ten millimoles of the amide was then dissolved in methanol; 11 mmol of methyl iodide was then added, and the solution was allowed to reflux for 3 h. The resulting precipitate was then collected by filtration and dried. The pyridinium salt was reduced as previously described.

The 3-quinolinecarboxamide and 4-isoquinolinecarboxamide were prepared according to literature procedures,[14] quaternized with methyl iodide, and reduced as previously described.

Kinetic Analysis. The rate of ferricyanide-mediated oxidation of various dihydropyridines was determined using a modification of published methods. In this procedure, the rate of decrease of the band III absorbance (~360 nm) was determined in buffered 20% aqueous acetonitrile solutions [0.1 mM $K_4Fe(CN)_6$, 60 mM KCl, and 1.0 mM K_2CO_3] containing various concentrations of $K_3Fe(CN)_6$ (1-50 mM). The dihydropyridine in acetonitrile was added to the test solutions using a Hamilton syringe. The solutions were maintained at 37 °C in a thermostated cell holder and contained in anerobic screw-top cuvettes (Spectrocell, Inc.) fitted with Teflon septa. For a given ferricyanide concentration, the pseudo-first-order rate constant was determined, and then these values were plotted as a function of ferricyanide ion concentration, generating a slope from which the second-order rate constant (k_0 s^{-1} M^{-1}) was obtained.

In all of the kinetic studies, solutions were prepared with water that had been boiled for 1 h and cooled with a stream of helium passing through it. Throughout the studies, the oxidation of 1-benzyl-1,4-dihydronicotinamide (**17**) was used to confirm the integrity of ferricyanide solutions since oxygen is known to affect the rates of reaction. Acceptable second-order rates for this reaction were 2.25 ± 0.25 s^{-1} M^{-1}. If the rate fell outside of this range, new solutions were prepared. In all cases slopes were linear ($r > 0.995$).

In two cases the extremely slow rate of oxidation (compounds **19** and **20**) prompted the use of HPLC rather than UV analysis. In these circumstances, four different concentrations of ferricyanide (4, 6, 8, and 10 mM) in buffer were prepared as before. At time $t = 0$, the dihydropyridines were added to these solutions and then sampled every 3 h for 100 h. Both compounds could be analyzed with the same mobile phase (70:30 acetonitrile-H_2O) flowing at 1 mL/min. Separation was achieved on a Spherisorb C-18 Alltech Associates/Applied Science 4.6 mm i.d. × 25 cm reversed-phase column operating at ambient (26 °C) temperatures. The retention times for **19** and **20** in this study were 7.0 and 7.8 min, respectively. Samples were provided in duplicate, and each sample was analyzed twice. As in the previous section, slopes were linear ($r > 0.999$).

Supplementary Material Available: Compound characterization data (2 pages). Ordering information is given on any current masthead page.

Highly Stereoselective Synthesis of Chiral Alkylallenes by Organocopper(I)-Induced Anti 1,3-Substitution of Chiral Propynyl Esters[1,2]

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The synthesis of chiral 1,3-dialkylallenes $R^1CH{=}C{=}CHR^2$ of high enantiomeric purity, by applying homogeneous reactions between organocopper(I) reagents of the type [{R^2CuX}$MgX{\cdot}LiX$] and chiral propynyl methanesulfonates or sulfinates at low temperatures in THF, is reported. The reactions are generally fast; typically complete conversion is obtained within a few minutes at -60 °C. Overall, high anti stereoselectivity is observed. A plausible mechanism is put forward, and comparison is made with the stereochemistry of reactions of comparable substrates with d^{10} complexes, e.g. of Pd(0).

Introduction

During the last decade a revival in the synthesis of optically active allenes can be noted.[3] This renewed interest can also be deduced from the recent successful efforts to implement chiral NMR probes for the assessment of enantiomeric purity of (in this respect thusfar elusive) 1,3-dialkylallenes and trialkylallenes.[4]

In 1978 Tadema et al. reported on the efficient synthesis of chiral phenylallenes from 1-phenylprop-2-yn-1-yl esters by applying organocopper(I) reagents.[5] The stereochemistry of the 1,3-substitution involved (see Scheme I) was disputed at first, but it could be unambiguously shown by X-ray crystallography that methylcopper(I) induces stereospecific anti 1,3-substitution in steroidal substrates,[6] in accord with an early proposal by Crabbé c.s.[7] Meanwhile, several more or less successful approaches to chiral allenes have appeared in the literature.[3,8-11] Most of these rely on the same reaction principle but, despite their well-known tendency to racemize chiral allenes,[8] di-

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