On the Mechanism of the Reduction of α-Halo Ketones by Several Models for NADH. Reduction by a SET-Hydrogen Atom Abstraction Chain Reaction[1]

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The mechanism for the reduction of the α-haloacetophenones by four dihydronicotinamides (DHNA's) proceeds by a free radical chain whose initiation and propagation sequences both contain single electron transfer reactions. The use of DHNA's as models for the role of NADH in enzyme-mediated reductions is discussed.

Introduction

Despite the importance of the 1,4-dihydronicotinamides, NADH and NADPH, in biochemical oxidation and reduction transformations, the mechanism for these reactions continues to be debated.[4] The key mechanistic question is whether the hydrogen transfer between the coenzyme and the substrate carbonyl occurs as a single-step hydride transfer (H^-),[5] a multistep electron transfer–hydrogen atom abstraction (e^-, $H^\bullet$),[6] or in a three-step sequence: an electron transfer; proton transfer; electron transfer (e^-, H^+, e^-).[7]

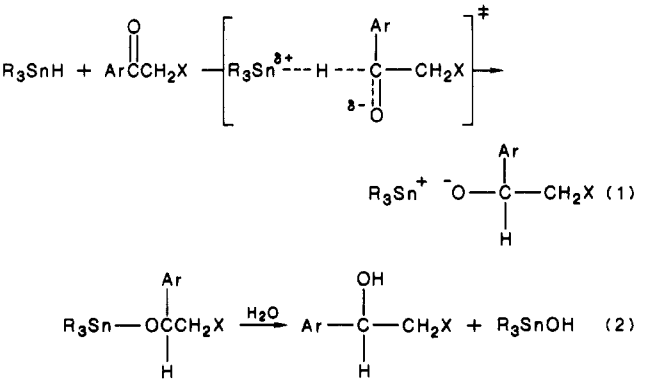
A large number of studies, using a variety of structurally different 1,4-dihydropyridines, on a variety of substrates, has been carried out to develop efficient NADH mimics. Although enzyme controlled NADH reductions are catalytic in the cofactor, which is itself catalytically regenerated, the 1,4-dihydropyridines have in the main been studied as reagents, reacting with substrates in stoichiometric amounts.

The most widely studied NADH models are the *N*-alkyl- and *N*-aryl-1,4-dihydronicotinamides. The use of these reagents has made it possible to carry out the reduction of structurally diverse substrates in nonaqueous solution.

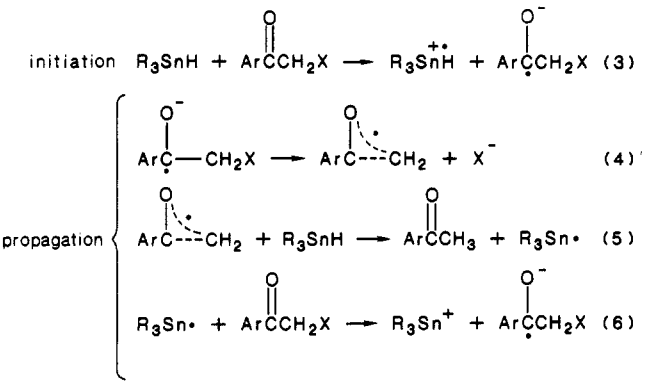
N-methylacridinium salts have been used by a number of workers as substrates to study the mechanism of dihydronicotinamide reductions in aprotic solvent. Powell and Bruice[5d] have investigated the kinetics of the reduction of *N*-methylacridinium iodide by 1-benzyl-1,4-dihydronicotinamide (I), BDNAH, (k_2 = 79.9 M^{-1} s^{-1}, 30 °C). From a study of the kinetic and product isotope effects resulting from the reaction of deuteriated and tritiated BDNAH, they concluded that the reduction proceeds by a hydride-transfer mechanism.

Ohno et al.,[7b] on the other hand, have used deuterium-labeled 1-aryl-1,4-dihydronicotinamides to study the kinetics of the reduction of *N*-methylacridinium iodide. They reported differences between the kinetic and product isotope effects and concluded that a multistep process (e^-, H^+, e^-) was responsible for the reduction.

Scheme I



Scheme II



In two cases BDNAH has been shown to reduce substrates by a radical chain process; the initiated reduction of tertiary and benzylic nitro compounds[8] and the photoinitiated reduction of benzyl bromide.[9] Although processes involving electron transfer have been invoked to explain the reduction mechanism of ketones by 1,4-dihydronicotinamides, to date no radical chain process has been proposed for the reduction by these reagents. Since a chain reaction appears to be incompatible with an enzyme-mediated reduction process,[10] the establishment of

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(10) The assumption that is generally made is that the rate-determining steps in the enzymatically controlled reductions are the binding and debinding of the cofaction.[1] Since a radical chain process imposes an additional slow step, the binding of a low concentration species, the substrate radical anion with the bound coenzyme in addition to the binding and debinding involved in the initiation step, a chain process would be expected to be far to slow to account for the enzymatic turn over times. A chain sequence would be unlikely to compete with other enzymatically controlled processes given normal radical life times and concentrations.

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Table I. Reduction of α-Haloacetophenone with BDNAH (I) in Acetonitrile

reacn	PhCOC-H_2X, X	conditions[a]	products yield, %[e] aceto-phenone	unreacted ketone
1	F[c]	hν, 96 h[b]	34.7 ± 0.8	34.3 ± 7.3
2		hν, no BDNAH, 96 h[b]	4.3 ± 0.1	59.6 ± 2.2
3		96 h		98.0 ± 2.0
4		96 h, AIBN (3%)		97.0 ± 1.0
5	Cl[d]	72 h	6.0 ± 1.0	74.1 ± 0.5
6		DNB (4%), 72 h	0.2 ± 0.2	63.4 ± 0.8
7		AIBN (3%), 72 h	68.7 ± 2.1	13.2 ± 0.7
8	Br[d]	24 h	10.6 ± 2.3	86.5 ± 0.5
9		DNB (4%), 24 h	4.0 ± 0.1	60.7 ± 2.3
10		AIBN (3%), 24 h	84.8 ± 5.8	0.0

[a] 61 °C. [b] 20 °C. [c] [Ketone]/[DHPA], 1:4. [d] [Ketone]/[DHPA], 1:2. [e] The values quoted are averages of two or more independent experiments.

chain reduction would tend to invalidate model studies with these reagents and substrates.

Recently we have reported the results of the reduction of a series of α-halo ketones with triorganotin hydrides.[11,12] The reductions were shown to proceed by two differentiable mechanistic pathways, both heterolytic hydride transfer [Scheme I (H^-)] and a homolytic electron transfer–hydrogen atom transfer chain reaction [Scheme II (e^-, $H^\bullet$)].

The parameters varied to differentiate between the two processes were the ease of oxidation of the hydride or its radical (Ph_3SnH > n-Bu_3SnH, $Ph_3Sn^\bullet$ > n-$Bu_3Sn^\bullet$), the ease of reduction of the substrate ($PhCOCH_2Br$ > $PhCOCH_2Cl$ > $PhCOCF_3$ > $PhCOCH_2F$ > $PhCOCH_3$), or the solvating power of the solvent used (methanol > acetonitrile > benzene). Appropriate combinations of the three determined the pathway followed by the reduction. The homolytic reactions, if they occurred, were found to be faster than the heterolytic reactions since the products were formed by a chain process. Since the mechanistic probes can clearly differentiate between the two processes, they were ideally suited to differentiate between the pathways followed by the *N*-alkyl- and *N*-aryl-1,4-dihydronicotinamides in ketone reductions.

Results

The reductions of α-fluoro-, α-chloro-, and α-bromoacetophenone with BDNAH (I) were carried out in acetonitrile (see Table I). The reactivity of the halides follows the same order as reported previously for their reduction by tin hydride.[1,12] Under the standard reaction conditions (acetonitrile, 61 °C, 96 h) the fluoride was found to be unreactive. The reactivity of three other dihydropyridines were compared with that of BDNAH for the reduction of the most reactive phenacyl halide, α-bromoacetophenone (see Table II). The reactivity of the 1,4-dihydropyridines studied could be screened by determining their polarographic half-wave oxidation potentials (see Table III).

To establish that the initiation process involved an electron transfer, 2,6-di-*tert*-butyl-1,4-benzoquinone, a ketone which forms a stable radical anion, was allowed to react with BDNAH. In both acetonitrile and Me_2SO the ESR spectrum of the radical anion was obtained.

Since *N*-[(*R*)-α-methylbenzyl]-1-propyl-1,4-dihydronicotinamide, PDNAH, had a lower oxidation potential than the other DHNA's, its reactivity with both phenacyl fluoride and phenacyl chloride was also investigated (see Table IV). The fluoride, which is unreactive with BDN-

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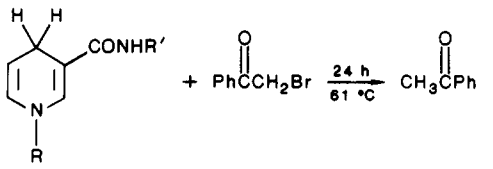
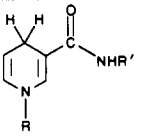
Table II. The Reduction of α-Bromoacetophenone with Several DHNA Derivatives[a] in Acetonitrile



reacn	R	R'	conditions	yield, %[b]
11	C_6H_5	H		4.0 ± 0.8
12			AIBN (3%)	26.4 ± 0.3
13			DNB (4%)	0.4 ± 0.3
14	$C_6H_5CH_2$	H		11.1 ± 1.1
15			AIBN (3%)	60.5 ± 1.3
16			DNB (4%)	0.9 ± 0.1
17	n-C_3H_7	H		21.9 ± 0.8
18			AIBN (3%)	68.9 ± 1.1
19			DNB (4%)	1.0 ± 0.3
20	n-C_3H_7	$CH(CH_3)Ph$		31.8 ± 2.5
21			AIBN (3%)	75.2 ± 0.4
22			DNB (4%)	1.4 ± 0.3

[a] [Ketone]/[DHNA], 1:2. [b] The values quoted are averages of two or more independent experiments.

Table III. Polarographic Half-Wave Potentials[a] for the Oxidation and Reduction of DHNA's and Substrate Ketones



DHN

R	R'	$E_{1/2}$, V
C_6H_5	H	+0.48
$C_6H_5CH_2$	H	+0.39
n-C_3H_7	H	+0.32
n-C_3H_7	$PhCH(CH_3)$	+0.28

X	$E_{1/2}$, V
H	−2.18
F	−1.85
Cl	−1.49
Br	−0.78

[a] $Ag/Ag^+ClO_4^-$ (0.1 M) reference electrode.

Table IV. The Reduction of α-Fluoro- and α-Chloroacetophenone by *N*-[(*R*)-α-Methylbenzyl]-1-propyl-1,4-dihydronicotinamide (IV), PDNAH (61 °C)

reacn	PhCOC-H_2X, X	conditions	products, %[c] $PhCOCH_3$	PhCH-(OH)-CH_2X[d]
22	F[a]	CH_3CN	2.2 ± 0.9	
23		CH_3CN, DNB (4%)	1.6 ± 0.2	
24		CH_3CN, AIBN (3%)	3.3 ± 0.3	
25	F[a]	CH_3OH	7.6 ± 0.3	3.7 ± 0.0
26		CH_3OH, DNB (4%)	4.8 ± 2.0	2.6 ± 0.6
27		CH_3OH, AIBN (3%)	54.2 ± 1.0	1.8 ± 0.8
28	Cl[b]	CH_3CN	8.8 ± 0.2	
29		CH_3CN, DNB (4%)		
30		CH_3CN, AIBN (3%)	79.0 ± 2.0	
31	Cl[b]	CH_3OH	11.3 ± 0.9	
32		CH_3OH, DNB (4%)	6.6 ± 0.2	
33		CH_3OH, AIBN (3%)	94.4 ± 1.4	

[a] [Ketone]/[PDNAH], 1:4; 96 h. [b] [Ketone]/[PDNAH], 1:2; 72 h. [c] The values quoted are averages of two or more independent experiments. [d] [α] = (+).

Scheme III

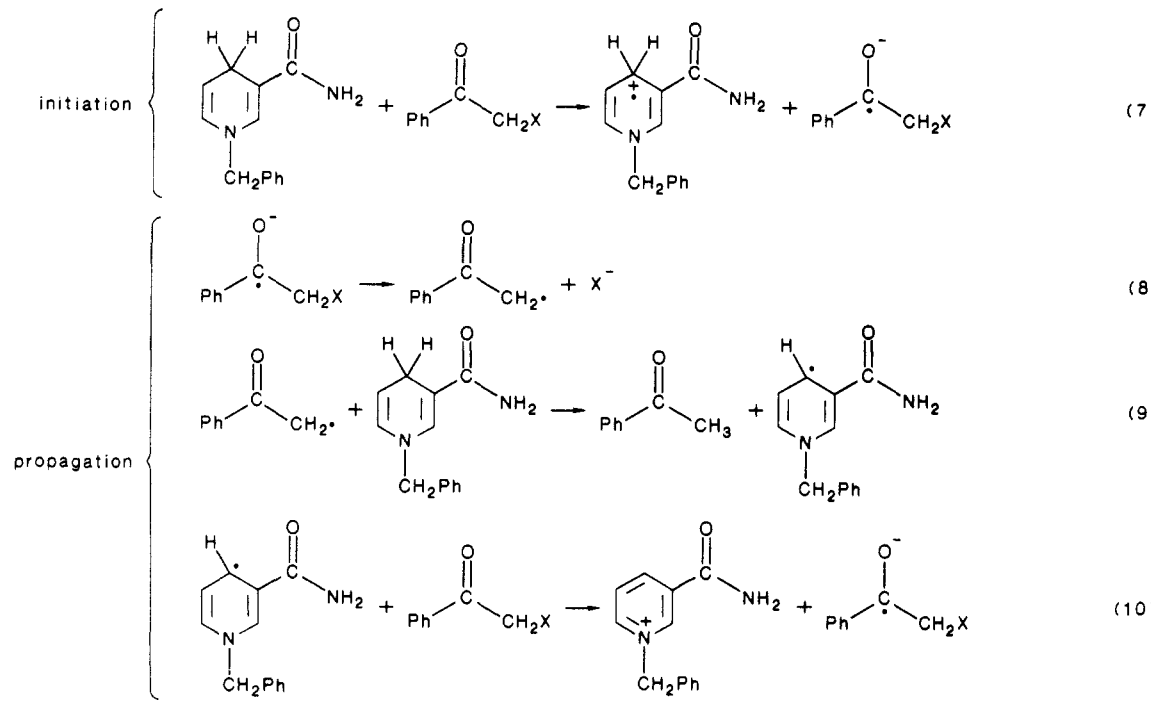


Table V. The Reduction of α-Fluoroacetophenone by *N*-Benzyl-1,4-dihydronicotinamide in Methanol (61 °C, 96 h)

		products, %[b]	
reacn	conditions[a]	$PhCOCH_3$	$PhCH(OH)CH_2F$
34		0.7 ± 0.2	1.4 ± 0.2
35	DNB (4%)	0.0	0.58 ± 0.08
36	AIBN (3%)	35.5 ± 0.5	0.0

[a] [Ketone]/[BDNAH], 1:4. [b] The values quoted are the averages of two or more independent experiments.

AH in acetonitrile, was reactive in the more polar solvent, methanol. With the more reactive PDNAH, however, the fluoride showed reaction in both solvents (see Table V). In the more solvating solvent, a small amount of the heterolytic reduction product, 2-fluoro-1-phenylethanol was also formed (see Tables IV and V). The reduction of a more reactive ketone, α-chloroacetophenone, with the more reactive substrate, PDNAH, in methanol, did not yield chlorohydrin, the sole product was acetophenone (see Table V).

Discussion

Free Radical Chain Reduction. An examination of the results obtained from the reduction of the three haloacetophenones with BDNAH in the relatively nonpolar solvent acetonitrile clearly establishes that the reductions of the chloride and bromide proceed via a free radical chain mechanism (see Table I). A molecule-induced homolysis, initiation process, initiates the reaction, while small amount of *m*-dinitrobenzene (*m*-DNB) (reactions 6, 9) inhibits and azobisisobutyronitrile (AIBN) (reaction 7, 10) initiates the chain (see Scheme III). From the data in Table I, assuming an initiator efficiency[13] of 0.5 and a half-life from decomposition[14] of AIBN of 24 h at 61 °C, a chain length, γ, was calculated for the reduction of α-chloroacetophenone (γ = 25) and α-bromoacetophenone (γ = 50).

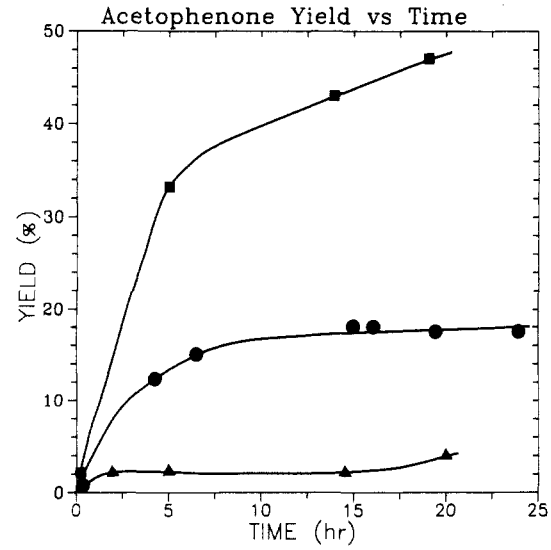


Figure 1. The reduction of α-bromoacetophenone (0.055 M) by BDNAH (0.101 M) in acetonitrile-d_3 (61 °C): (■) with added AIBN (3%); (▲) with added DNB (1.1%); (●) without additives.

A visual demonstration of the change in velocity of both the initiated and inhibited reactions can be obtained by following, with NMR spectroscopy, the production of acetophenone as a function of time (see Figure 1). Both inhibition and initiation are clearly demonstrated.

Initiation by electron transfer was demonstrated by allowing BDNAH to react with 2,6-di-*tert*-butylbenzoquinone, a ketone which forms a stable radical anion upon electron transfer. The coupling constants, a^H = 1.51 (CH_3CN) and a^H = 1.95 (Me_2SO) [g = 2.0054] for the three-line spectra were within experimental error the same as was reported previously for the radical ion generated both chemically and electrochemically.[15]

The observation that α-fluoroacetophenone was unreactive was quite informative. Although the reaction could be photoinitiated (reaction 1), presumably by a

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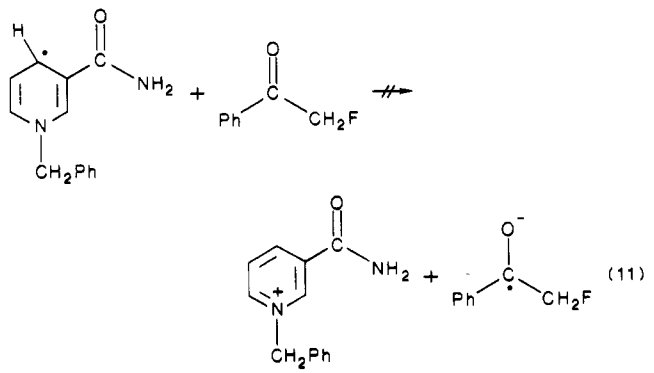
nonchain process, it could not be initiated with AIBN (reaction 4), unlike the other two halo ketones. The lack of reactivity is consistent with the inability of the dihydropyridyl radical to carry the chain by a SET process with the least reactive ketone (eq 11).



(11)

The conditions used to examine the reactions of each substrate were not those which ensured the optimum yields, but rather those which allowed the observation of the results of both the initiation and inhibition reactions. The material balance in some cases is not quantitative, but the analytical techniques clearly established the presence or absences of both homolytic and heterolytic reduction products, and in all cases control experiments established that both anticipated products were stable to the reaction conditions. As was the case in the reduction by triphenyltin hydride, the reduction using BDNAH followed the reactivity order $PhCOCH_2F < PhCOCH_2Cl < PhCOCH_2Br$.

During the investigation of the reduction of the α-halo ketones with trialkyltin hydrides, it was found that the structure of the reagent also determined the ability of the hydride or its radical to undergo SET with the α-halo ketones ($Ph_3SnH > Bu_3SnH$).[11] To probe this relationship, the reactions of several other substituted DHNA's were investigated with the most reactive of the phenacyl halides, under a standard set of conditions (see Table II). As expected, N-substitution with electron-donating alkyl groups increases the reactivity by substitution on either the ring nitrogen and/or the amide nitrogen. Electron-withdrawing phenyl substituents retard the formation of a positively charged radical cation or pyridinium salt. Likewise, the electron-withdrawing ability of the amide group is reduced by N-alkylation (reactions 11, 14, 17, 20). All four of the DHNA's reduce α-bromoacetophenone by a free radical chain reaction: they show initiation by small amounts (3%) of AIBN (reactions 12, 15, 18, 21) and inhibition by *m*-DNB (4%) (reactions 13, 16, 19, 22).

Evaluation of Reactants. The reactivity of the reducing agents and their ease of electrochemical oxidation was compared. The apparent reactivity of the DHNA's, corresponds directly to their ease of oxidation (see Tables I and III). Although the polarographic half-wave potentials resultant from irreversible surface-mediated oxidation cannot be considered to give kinetically (or thermodynamically) accurate potentials for electron transfer, they do appear to be useful, as do the reduction potentials of the halo ketones, in estimating their expected reactivities. The use of irreversible $E_{1/2}$ values to estimate the ability of a homologous series of compounds to participate in electron-transfer process has been previously successfully used.[9,16,17] By knowing the oxidation and reduction half-wave potentials it was possible to predict which reductions were likely to be successful. Since I was not able to reduce α-fluoroacetophenone, a more reactive reductant, IV, was chosen to achieve homolytic reduction (see Table IV).

Conclusions. The mechanism for the reduction of the α-haloketones by DHNA's proceeds by a free radical chain process. Since a chain mechanism appears to be incompatible with the enzyme-controlled reduction[10] it appears that the use of DHNA's as mimics for the enzyme-mediated reductions is not satisfactory to model the coenzymes activity. Furthermore, with a change in substrate, DHNA, and/or solvent, reactions 25–27 and 34–36, there is an indication that the mechanism for the reduction may even be changed from a homolytic toward a heterolytic pathway. The same behavior has been noted previously in the reports of the tin hydride reductions of these substrates.[11,12] The conflicting conclusion reached from the reduction of the acridinium salts by BDNAH[5d] and PDNAH[7b] at first appeared to be the result of a change in mechanism caused by changing the structure of the reagent, but it now appears that the structure of the reactant, the acridinium salt, is the governing factor which controls the reaction and militates its function as a heterolytic reductant.[17] The reductions of acridinium salts by NADH models, as are the reductions of the α-haloacetophenones, are of interest in themselves but appear to give no conclusive mechanistic information about the mechanism involved in enzyme-mediated reductions.

Experimental Section

Materials. Reagent (HPLC grade) acetonitrile (Caledon) was purified by the standard procedure.[18]

The internal standard for GLPC *p*-di-*tert*-butylbenzene (Aldrich), mp 78–79 °C (lit.[19] mp 80 °C), was recrystallized from ethanol and dried under vacuum over P_2O_5 (55 °C).

α,α'-Azoisobutyronitrile (Aldrich) was recrystallized from ethanol–water and dried under vacuum over P_2O_5, mp 101–102 °C (lit.[20] mp 103 °C).

m-Dinitrobenzene (Fisher) was recrystallized from ethanol, mp 89 °C (lit.[20] mp 88–90 °C).

Acetophenone (Fisher) was distilled at 93–95 °C (10 mm) [lit.[19] 202.6 °C (760 mm)].

α-Fluoroacetophenone was prepared by treating fluoroacetyl chloride with benzene in the presence of aluminum trichloride.[21] Fractional distillation at 70–72 °C (1.5 mm) [lit.[21] 65–70 °C (1 mm)] gave the product in 81% yield: mp 26–27 °C (lit.[21] mp 27–28 °C); NMR ($CDCl_3$) δ 5.57 (d, 2 H, J = 47.5 Hz), 7.36–8.10 (m, 5 H); IR (neat) 5.86 μm (CO); MS, *m/e* 138, 105.

α-Chloroacetophenone (Aldrich) was recrystallized from methanol, mp 53–54.5 °C (lit.[20] mp 54–56 °C).

α-Bromoacetophenone (Aldrich) was recrystallized from methanol, mp 49–51 °C (lit.[20] 48–51 °C).

1-Benzyl-1,4-dihydronicotinamide was prepared according to the literature procedure:[22] mp 119–121 °C dec (lit.[22] mp 120–122 °C dec); NMR ($CDCl_3$) δ 3.05 (m, 2 H), 4.30 (s, 2 H), 4.72 (m, 1 H), 5.60 (s, 2 H), 5.86 (m, 1 H), 7.0 (d, 1 H), 7.25 (m, 5 H).

1-Phenyl-1,4-dihydronicotinamide was prepared by an exchange reaction with 1-(2,4-dinitrophenyl)-3-carbamoyl pyridinium chloride and aniline followed by reduction:[23] mp 100 °C dec (lit.[23] mp 100 °C dec); NMR ($CDCl_3$) δ 3.20 (m, 2 H), 4.90 (m, 1 H), 5.61 (s, 2 H), 6.32 (m, 1 H), 7.20 (m, 5 H), 7.51 (d, 1 H).

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1-Propyl-1,4-dihydronicotinamide was prepared according to the literature procedure:[24] mp 87 °C dec (lit.[24] mp 86 °C dec); NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.61 (q, 2 H), 3.14 (m, 4 H), 4.76 (m, 1 H), 5.60 (s, 2 H), 5.75 (m, 1 H), 6.92 (d, 1 H).

N-[(*R*)-α-Methylbenzyl]-1-propyl-1,4-dihydronicotinamide was prepared according to the literature procedure:[24] mp 111 °C dec (lit.[24] mp 110 °C dec); NMR ($CDCl_3$) δ 0.91 (t, 3 H), 7.55 (m, 5 H), 3.05 (t, 2 H), 3.15 (m, 2 H), 4.70 (d, 1 H), 5.4 (s, 2 H), 5.75 (d, 1 H), 6.78 (d, 1 H), 7.30 (m, 5 H); $[\alpha]^{20}_D$ -172.3° (CH_3CN) [lit.[24] $[\alpha]^{20}_D$ -172.9° (CH_3CN)].

General Procedure for the Reduction of the α-Halo Ketones. An aliquot of a solution of DHNA (0.10 M) (or for the reactions of the α-fluoro ketone, 0.20 M), the ketone (0.050 M), and the additive was placed in a Pyrex reaction ampule, degassed, and sealed under vacuum. When the reaction was catalyzed by irradiation a 275 watt G.E. Sunlamp was used, and the mixtures were thermostated in a Pyrex water bath. In the dark reactions the ampule was thermostated in an oil bath at 61 °C for the appropriate time. After the required reaction time, the ampule was opened, and a aliquot solution of the internal standard (0.04 M) was added. The product mixture from the reduction of the fluoro ketone was analyzed by GLPC using a 20 ft × $^1/_4$ in. glass column packed with 10% FFAP on Chromosorb WAW DMCS, 60/80 mesh, or for the other halo ketones a 20 ft × $^1/_4$ in. glass column packed with 5% OV-101 on Chromosorb WAW DMCS, 100/120 mesh. GLPC analyses were carried out with a HP 5840 A gas chromatograph interfaced to a HP 5840 A integrator. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves constructed from known mixtures.

Products were identified by a comparison of their retention times, GLPC-mass spectra, GLPC-IR, and ^{1}H NMR with those of authentic samples. Duplicate experiments were run with each ketone.

The internal standard, 1,4-di-*tert*-butylbenzene, and the anticipated products from both the homolytic and heterolytic reactions were added to the solvent, degassed, sealed, and thermostated, 61 °C, for the required time. A GLPC analysis of the mixture showed that the products were stable under the reaction conditions.

Polarographic Reduction and Oxidation. The current-voltage curves for the polarographic reductions of the ketones and the oxidation of the dihydronicotinamides were obtained with a Princeton Applied Research (PAR) Model 174 A polarograph interfaced with a PAR 303 DME. The solutions were anhydrous acetonitrile containing $(Bu)_4N^+ClO_4^-$ (0.1 M) and the reactant (0.01 M). The $E_{1/2}$ values relative to $Ag/AgClO_4$ (0.1 M) are listed in Table III.

ESR Spectroscopy. The ESR spectra were obtained for the radical anion of 2,6-di-*tert*-butylbenzoquinone by allowing a solution 4.9×10^{-2} M in the quinone and $4.7\text{-}10.4 \times 10^{-2}$ M in BANAH to stand at room temperature for several minutes. The intensity of the signals grew with time and appeared to be persistent for days. A Brucker ER 200 E/D spectrometer was used to record the spectra.

NMR Studies of the Reaction Velocity. A degassed acetonitrile-d_3 solution (0.101 M) in BANAH and (0.055 M) in α-bromoacetophenone and 0.020 M in 1,4-di-*tert*-butylbenzene as an internal standard was allowed to react in the cavity of a Brucker 200-MHz ^{1}H NMR spectrometer, whose probe was thermostated at 61 °C. The integrated signals at δ 1.27 and 2.55 corresponded to the methyl protons of the internal standard and acetophenone, respectively, were recorded as a function of time. A plot of the results is given in Figure 1.

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Substituent Effects on the Redox Chemistry of Anthracycline Antitumor Drugs

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Reduction of 11-deoxydaunomycin (**8**), adriamycin (**1**), 4-demethoxydaunomycin (**9**), and 4-methoxy-6-deoxydaunomycin (**10**) with *meso*- and *d,l*-3,3',5,5,5',5'-hexamethyl-2,2'-dioxo-3,3'-bimorpholinyl (**3** and **4**) is described. Quinone methide intermediates from glycosidic cleavage of reduced **1**, **8**, and **9** were characterized by UV-vis spectroscopy and the rate constants for their tautomerization to the respective 7-deoxyaglycons were determined. These rate constants together with those from earlier measurements, ranging from 0.013 to 0.000 095 s^{-1}, establish an order of nucleophilicity of the quinone methides from reductive glycosidic cleavage of five anthracyclines of biological interest. The dimerization of the quinone methide from reduction of 11-deoxydaunomycin was established and the rate constant determined for comparison with the rate constant for dimerization of the quinone methide from reduction of aclacinomycin A. Reduction of **10** did not yield glycosidic cleavage but only catalysis of the disproportionation of **4** most likely by hydride transfer from the hydroquinone of **10** to 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**5**), the product of oxidation of **4**. The rate constant for hydride transfer was measured as a function of pH and compared with the rate constant for hydride transfer from 7-deoxydaunomycinone hydroquinone to **5**.

Introduction

Adriamycin (**1**) and daunomycin (**2**) are clinically important anthracycline antitumor drugs produced by mutant strains of *Streptomyces peucetius*.[1,2] Since their discovery extensive investigation of their chemical and biochemical reactivity has occurred. These studies have in part been directed to the discovery of derivatives or methodology which will maximize tumor response and minimize side effects, especially the acute cardiotoxicity. An excellent recent review has been published by Abdella and Fisher.[3] The in vivo and in vitro redox chemistry of the drugs is complex and appears to be involved in the

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