256 (1130); f = 0.035 for 290–256 nm; UV (in 2E) λ_{max} 277 nm (ϵ 3900). Our spectrum in 96E differs rather strongly from that given in ref 4 [λ, nm (ϵ reference, ϵ present work): λ_{max} 278 (4900, 4090), 270 (3800, 3200); λ_{min} 255.5 (~1600, 1070)]. Our sample is probably less contaminated by more strongly absorbing impurities: UV max (50E, 4.5 M H_2SO_4) 274.5 nm (ϵ 1590), 266.5 (1320); min 270 (950), 256 (850); f = 0.019 for 290–250 nm.

N,N-Dimethylaniline (**5**):[5] UV max (in 0.01 M HCl) 264 nm (ϵ 102), 254 (205), 248.5 (169); min 262.5 (85), 250.5 (152), 222 (23); f = 0.033 for 290–222 nm. In 50E, 0.26 M HCl, f = 0.0030 nm. *N*-Methyldiphenylamine (**6**):[21] bp 124 °C (1.5 mm); UV max (in 2E) 286 nm (ϵ 8230), 243 (8160); min 258 (5970), 223 (6530); f = 0.210 for 350–258 nm, f = 0.188 for 258–223 nm; UV max (50E) 292 nm (ϵ 10600), 245 (8920); min 261 (4770), 224 (5570); f = 0.232 for 350–261 nm; f = 0.184 for 261–224 nm; UV max (10E, 6.5 M HCl) 265.5 nm (ϵ 344), 255.5 (546), 249.5 (479); min 264 (320), 252 (447), 233 (265); f = 0.0100 for 300–233 nm. In 50E, 4.5 M H_2SO_4, f = 0.0073 for 300–233 nm. Triphenylamine (**7**) was recrystallized from 96E: mp 128–129 °C; UV max (4E) 312 nm (ϵ 20200), min 265 (7800); f = 0.66 for 600–265 nm. The solutions are light-sensitive. In 2E, 13 M HCl (Merck GR): UV max 294 nm (ϵ 220), 261 (645), 256 (770), 251 (750); min 275 (150), 260 (640), 253 (680), 237 (530); f = 0.0048 for 350–275 nm, f = 0.0141 for 275–237 nm. In all probability the band around 300 nm (at $H_o''' \approx -5.9$) is due to free amine; the (light blue) solution in 10.5 M H_2SO_4 ($H_o''' \approx -6.9$[22]), is, initially, optically empty at this wavelength. Sulfuric acid and phosphoric acid give light blue solutions[23] the spectra of which change rapidly. Perchloric acid gives deep blue solutions instantaneously,[23] probably containing the radical cation [max at 710 nm (ϵ ~40000)]. One HCl bottle out of ten also gave a light blue solution.

Triphenylmethane was recrystallized from ethanol: mp 93–93.5 °C; UV max (50E) 270 nm (ϵ 628), 262 (891); min 268 (528), 241 (348); f = 0.0134 for 290–241 nm. The spectrum in 50E, 6 M HCl is almost identical.

Determination of pK_a Values. Three methods can be distinguished. Most values were obtained by the potentiometric method described earlier;[24] for **1** a Beckman Enduraglas electrode was used to avoid sodium ion corrections. As indicated in Table I, some of the lower pK_a values were determined on the basis of an acidity function. The third method, denoted as the SP method, gives $pK_a = R - \Delta + \log(BH^+/B) + \log y$, where R is the pH meter reading, Δ is the solvent correction of this reading,[24] BH^+/B is the spectrophotometrically determined ratio of conjugate acid and base, and $\log y$ is the Debye–Hückel correction.[24] For example, a 2×10^{-5} M solution of **4** in 50E, 0.194 M HCl with R = 0.99, Δ = 0.17, $\log(BH^+/B)$ = –0.179, and $-\log y$ = 0.213, gives pK_a = 0.428. The value in Table I is the average (SD 0.02) of four measurements at 270 nm and four measurements at 278 nm, with $\log(BH^+/B)$ ranging from –0.53 to +0.69. In 30.7E and 9.6E the corrections are smaller; in 9.6E, Δ = 0.05, and $-\log y$ of the four solutions ranges from 0.06 to 0.14. In our experience the SP method works well down to pH meter readings of about 0.5.

Registry No. **1**, 100-76-5; **2**, 4363-25-1; **3**, 4378-82-9; **4**, 197-45-5; **5**, 121-69-7; **6**, 552-82-9; **7**, 603-34-9; triphenylmethane, 519-73-3.

(21) Okawa, M.; Sawakuri, Y. *Jpn. Kokai Tokkyo Koho* 74124037; *Chem. Abstr.* **1975**, *82*, 155725.
(22) Arnett, E. M.; Mach, G. W. *J. Am. Chem. Soc.*, **1964**, *86*, 2671. Reference 10.
(23) Cf.: Kemmitt, R. D. W.; Nuttall, R. H.; Sharp, D. W. A. *J. Chem. Soc.* **1960**, 46.
(24) See: van Veen, A.; Hoefnagel, A. J.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 289. Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1978**, *43*, 4720 and papers cited therein.

Kinetics and Mechanism of the Reaction of 5-Nitroisoquinolinium Cations with 1,4-Dihydronicotinamides

John W. Bunting* and Shinta Sindhuatmadja

Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Received January 22, 1981

The kinetics of the reduction of 2-methyl- (**7**) and 2-(Z-benzyl)-5-nitroisoquinolinium cations (**2**) by 1-(X-benzyl)-1,4-dihydronicotinamides (**1**) to give the corresponding 1,2-dihydro-5-nitroisoquinolines have been studied in 20% acetonitrile–80% water (v/v) at pH 7.0, 25 °C, and an ionic strength of 1.0. Deuterium labeling studies indicated direct hydrogen transfer from C-4 of **1** to C-1 of **2** or **7** without exchange with solvent protons. In the presence of large excesses of the 5-nitroisoquinolinium cations, the reactions are cleanly first order in **1**. The pseudo-first-order rate constants (k_{obsd}) were evaluated as a function of the concentrations of **2** and **7** and were found to display kinetic saturation consistent with the rapid preequilibrium formation of 1:1 complexes between **1** and **2** or **7**. Association constants for complex formation were evaluated from the kinetic data; these constants are independent of X in **1** but strongly dependent on Z in **2**. These data require the presence of at least two types of 1:1 complex, at least one of which is nonproductive, in the reaction between **1** and **2**. Rate constants for hydrogen transfer were also calculated and shown to be closely correlated by the Hammett σ constants for X and Z. For **1**, ρ_x is the same for the reduction of **7** and **2** (i.e., ρ_x is independent of Z), while for **2**, ρ_z is independent of X within experimental error. Comparison of these kinetic ρ_x and ρ_z parameters with ρ values for equilibria which involve generation (or neutralization) of a unit positive charge in closely related systems allows evaluation of δ = 0.82 for the magnitude of the partial positive charge generated on the dihydronicotinamide moiety in the rate-determining transition state, and ξ = 0.38 for the fraction of positive charge neutralized on the isoquinolinium cation in this transition state. This discrepancy between δ and ξ indicates that the migrating hydrogen atom bears a –0.44 charge in the transition state and is thus clearly "hydridic" in character.

The nature of the detailed reaction mechanisms of enzymic reactions involving the nicotinamide coenzymes continues to be a major unsolved problem of bioorganic chemistry.[1-5] All such reactions formally involve the transfer of a hydride ion from the reduced form of the coenzyme (NADH or NADPH) to a suitable hydride-ac-

(1) Kill, R. J.; Widdowson, D. A. In "Bio-organic Chemistry"; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. IV, pp 239–275.
(2) Sigman, D. S.; Hajdu, J.; Creighton, D. J., ref 1, pp 385–407.
(3) Klinman, J. P. In "Isotope Effects on Enzyme-Catalyzed Reactions"; Cleland, W. W., O'Leary, M. H., Northrup, D. B., Eds.; University Park Press: Baltimore, MD, 1977; pp 176–208.
(4) Kurz, L. C.; Kurz, J. L. *Eur. J. Biochem.* **1978**, *90*, 283.

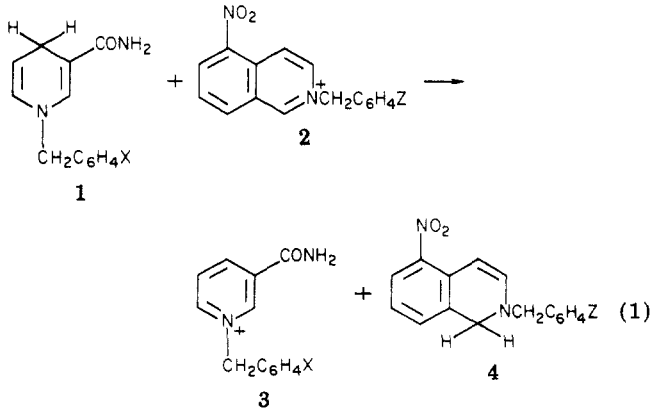
0022-3263/81/1946-4211$01.25/0

ceptor substrate or the chemical reverse of this process. There are basically three classes of possible reaction mechanisms for hydride transfer in such reactions: (i) one-step transfer of hydride ion, (ii) transfer of an electron and a hydrogen atom in two steps, (iii) transfer of two electrons and a proton in three steps. Consideration of the order of transfer indicates that each of ii and iii encompasses more than one discrete mechanism.

Conclusive evidence that allows an unambiguous choice among i–iii continues to be elusive for the enzymic reactions. The related nonenzymic reactions in which simple 1,4-dihydronicotinamides act as hydride donors toward suitable acceptor molecules have been the objects of many recent studies[1,2] as models for the corresponding enzymic reactions. Although a wide variety of hydride acceptors has been investigated, an unambiguous choice among mechanisms i–iii is still difficult to make in most cases.

There have been several recent investigations in which 1-benzyl-1,4-dihydronicotinamide has been used as a source of hydride in reductions of heteroaromatic cations. The studies of Sigman and co-workers[6-8] on the reduction of the 10-methylacridinium cation and of van Eikeren and co-workers[9] on the 1-benzyl-1,4-dihydronicotinamide–1-benzylnicotinamide cation transhydrogenation using suitable isotopic labels have both pointed to the possible generation of at least one intermediate species during these formal hydride transfers. These studies therefore throw doubt upon a direct hydride transfer although they do not allow a definite distinction between the mechanistic possibilities in ii and iii above. For the above two reactions, primary deuterium kinetic isotope effects do indicate that C–H bond breaking occurs in the rate-determining transition state.

We felt that a significant contribution might be made to unraveling the mechanistic ambiguities in such reactions if a suitable probe were available for the simultaneous monitoring of changes in electronic charge in each of the hydride donor and acceptor species upon proceeding to the rate-determining transition state. Such a probe is available if one investigates the influence of electronic substituent effects in both hydride donor and acceptor species upon the rates of the formal hydride-transfer reaction. We have chosen to attempt this approach via a detailed kinetic study of substituent effects upon the reduction of 2-(substituted benzyl)-5-nitroisoquinolinium cations by 1-(substituted benzyl)-1,4-dihydronicotinamides (eq 1). This



(1)

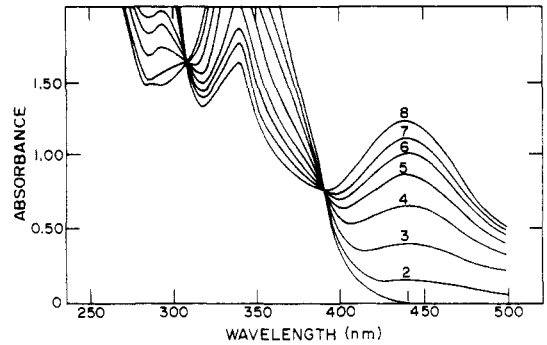
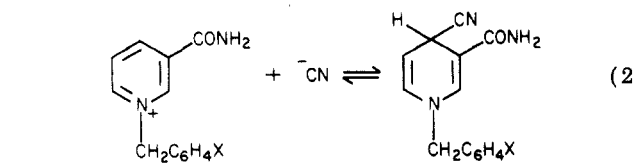
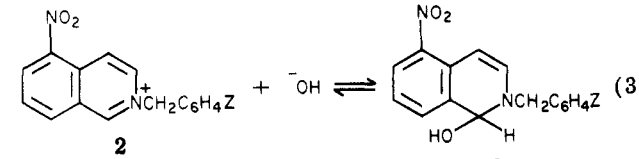


Figure 1. Time dependence of the electronic absorption spectrum of an equimolar (3×10^{-3} M) mixture of 1 (X = H) and 7 in 20% CH_3CN–80% H_2O at pH 7.0, ionic strength 1.0, and 25 °C (cell path length 1 mm). Curves 1–8 are obtained at 0, 3, 13, 30, 50, 72, 90, and 120 min, respectively.

reaction is attractive since substituent effects (as Hammett ρ values) upon equilibrium constants are available for reactions which involve charge neutralization in both nicotinamide cations[10] (cyanide ion addition (eq 2)) and



(2)

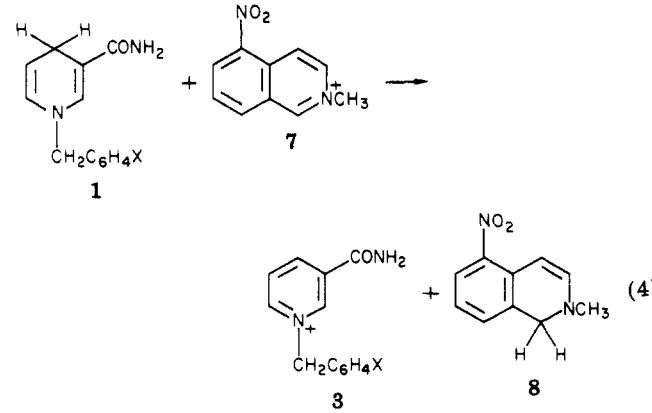


(3)

5-nitroisoquinolinium cations[11] (hydroxide ion addition (eq 3)). Comparison of kinetic ρ values based upon both X and Z substituents in reaction 1 with equilibrium ρ values for reactions 2 and 3 should give a direct insight into the extent of charge development on 1 and charge neutralization on 2 in the rate-determining transition state for reaction 1.

Results

We initially investigated the influence of substituents X in 1 upon the rates of reduction of 5-nitroisoquinolinium cations by using the *N*-methyl cation 7 as a hydride acceptor (eq 4).

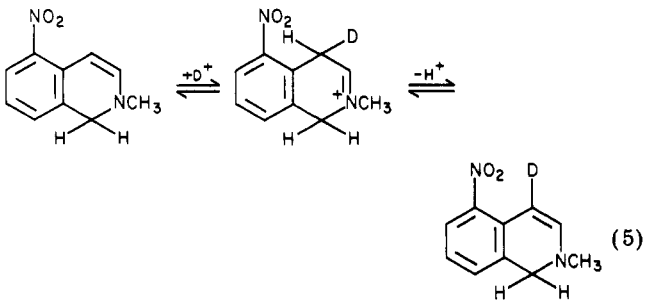


(4)

(5) Blankenhorn, G. In "Pyridine-Nucleotide-Dependent Dehydrogenases": Sund, H., Ed.; Walter de Gruyter: West Berlin, 1977; pp 185–205.
(6) Creighton, D. J.; Hajdu, J.; Mooser, G.; Sigman, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 6855.
(7) Hajdu, J.; Sigman, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 6060.
(8) Hadju, J.; Sigman, D. S. *Biochemistry* **1977**, *16*, 2841.
(9) van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 8057.
(10) Bunting, J. W.; Sindhuatmadja, S. *J. Org. Chem.* **1980**, *45*, 5411.
(11) Bunting, J. W.; Norris, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 1189.

The time dependence of the electronic absorption spectrum of a 1:1 mixture of 1 (X = H) and the bromide salt of 7 is shown in Figure 1. Clean isosbestic points indicate the absence of significant concentrations of any intermediate species. The development of an absorption maximum in the vicinity of 440 nm is characteristic of 1,2-dihydro-5-nitroisoquinolines.[11,12] Since the longest wavelength maximum in the spectrum of the 1-benzylnicotinamide cation is located at 266 nm, maxima in the product spectrum at longer wavelengths are due to the reduction product alone. The λ_{max} = 291, 339, and 439 nm thus assigned to 8 are in agreement with λ_{max} = 325 and 430 nm reported for 1,2-dihydro-1-hydroxy-2-methyl-5-nitroisoquinoline.[12] Similar spectral changes were observed during the reduction of all 5-nitroisoquinolinium cations by all 1,4-dihydronicotinamides and are consistent with all reduction products being the appropriate 1,2-dihydro-5-nitroisoquinolines.

The identity of 8 was further confirmed by mass spectrometry and ^{1}H NMR spectral analysis. A red solid which was isolated from the reduction of 7 by 1 (X = H) displayed a mass spectral molecular ion peak at m/e 190 and the following ^{1}H NMR spectrum in $CDCl_3$: δ 2.76 (3 H, s), 4.20 (2 H, s), 5.93 (1 H, d, $J_{3,4}$ = 8 Hz), 6.27 (1 H, d, $J_{3,4}$ = 8 Hz), 6.77 (1 H, quasi-triplet, $J_{6,7}$ = 7 Hz, $J_{7,8}$ = 7 Hz), 7.02 (1 H, dd, $J_{6,8}$ = 2 Hz, $J_{6,7}$ = 7 Hz), 7.73 (1 H, dd, $J_{6,8}$ = 2 Hz, $J_{7,8}$ = 7 Hz). The red product from the reduction of 7 by 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide displayed a molecular ion peak at m/e 191 and a ^{1}H NMR spectrum identical with that indicated above except that the singlet at δ 4.20 now integrated for only 1 H. Both of these observations indicate the incorporation of one deuterium atom at C-1 of the 1,2-dihydroisoquinoline product and show that the hydrogen atom that is transferred does not exchange with solvent protons during the reaction. This latter point was further confirmed by examination of the product from reduction of 7 by 1 (X = H) in 20% acetonitrile/80% D_2O. No incorporation of deuterium at C-1 occurred in this case since the singlet at δ 4.20 integrated for 2 H within experimental error. However, a modification of the ^{1}H NMR spectrum of the red product was observed in this case: the doublet at δ 5.93 assigned to the C-4 proton of 8 was missing while the signal at δ 6.27 assigned to the C-3 proton was present as a singlet rather than as the doublet reported above. Both of these spectral changes are readily explained by acid-catalyzed hydrogen exchange at the β-carbon atom of the enamine product as indicated in eq 5.



(5)

Since 8 is the only species in eq 4 which absorbs at 450 nm, the kinetics of this reaction may be conveniently monitored by following the time dependence of the absorbance at this wavelength. The increase in absorbance at 450 nm was kinetically first-order in dihydronicotinamide under conditions in which 7 was in 25–625-fold excess. Pseudo-first-order rate constants, k_{obsd}, for several X are shown in Figure 2 as a function of [7]. A kinetic saturation effect is clear. Double-reciprocal plots of these data (Figure 3) are linear and can be characterized by slope and ordinate intercept (Y_{int}) parameters. These parameters, as their reciprocals, are listed in Table I for the reduction of 7 by a variety of type-1 compounds.

Similar kinetic saturation curves were observed for the pseudo-first-order rate constants for the reaction of all 1-(substituted benzyl)-5-nitroisoquinolinium cations (2) by

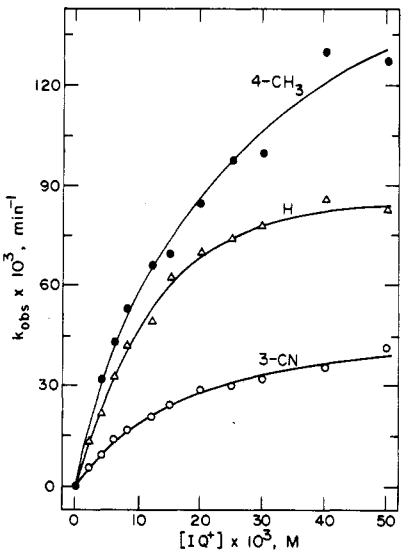


Figure 2. Pseudo-first-order rate constants (k_{obsd}) as a function of isoquinolinium cation concentration for reduction of 7 by 1 (X = 4-CH_3, H, 3-CN).

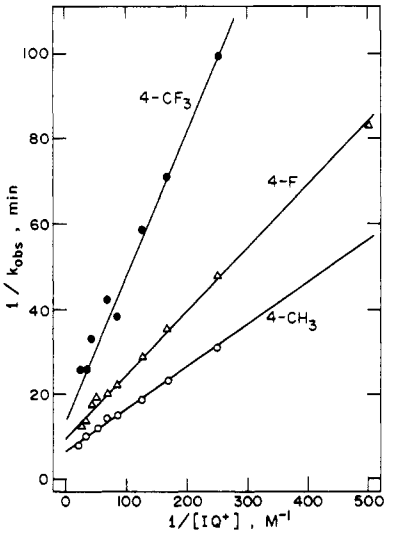


Figure 3. $1/k_{obsd}$ as a function of 1/[7] for reduction of [7] by 1 (X = 4-CH_4, H, 4-CF_3).

Table I. Parameters for Eq 6 for Reduction of 7 by 1[a]

X	1/slope	$1/Y_{int}$	Y_{int}/slope
4-CH_3	10.2 ± 0.7	0.16 ± 0.01	64 ± 4
H	7.1 ± 0.4	0.125 ± 0.006	57 ± 3
4-F	6.7 ± 0.3	0.105 ± 0.005	64 ± 3
4-Br	4.5 ± 0.3	0.081 ± 0.005	56 ± 4
3-F	3.8 ± 0.5	0.068 ± 0.008	56 ± 7
4-CF_3	3.1 ± 0.2	0.059 ± 0.005	52 ± 4
3-CN	3.1 ± 0.2	0.049 ± 0.002	64 ± 3
4-CN	2.3 ± 0.3	0.046 ± 0.005	49 ± 6

[a] 25 °C, ionic strength 1.0, pH 7.0, in 20% CH_3CN–80% H_2O. The units are as follows: 1/slope, M^{-1} min^{-1}; $1/Y_{int}$, min^{-1}; Y_{int}/slope, M^{-1}.

(12) Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1974**, *52*, 962.

Table II. Dependence of 1/Slope upon X and Z for Reduction of 2 by 1[a]

X	Z							
	4-CH_3	H	4-F	4-Br	3-F	4-CF_3	3-CN	4-CN
4-CH_3		25 ± 2						
H	24 ± 1	26 ± 1	27 ± 2	34 ± 3	37 ± 9	44 ± 9	50 ± 10	>18[b]
4-F		17 ± 3						
4-Br		13.9 ± 0.7						
3-F	12.0 ± 0.6	11.8 ± 0.6			21 ± 3		32 ± 5	28 ± 1
4-CF_3		8.4 ± 0.7						
3-CN		6.8 ± 0.6						
4-CN	8 ± 1	6.4 ± 0.5					19 ± 4	20 ± 3

[a] At 25 °C, ionic strength 1.0, and pH 7.0 in 20% CH_3CN–80% H_2O; units of M^{-1} min^{-1} for 1/slope. [b] k_{obsd} is independent of the concentration (≥1 mM) of 2 (Z = 4-CN).

Table III. Dependence of $1/Y_{int}$ upon X and Z for Reduction of 2 by 1[a]

X	Z							
	4-CH_3	H	4-F	4-Br	3-F	4-CF_3	3-CN	4-CN
4-CH_3		0.104 ± 0.009						
H	0.26 ± 0.01	0.108 ± 0.005	0.093 ± 0.008	0.21 ± 0.02	0.09 ± 0.01	0.13 ± 0.01	0.045 ± 0.009	0.018 ± 0.001
4-F		0.090 ± 0.010						
4-Br		0.063 ± 0.003						
3-F	0.24 ± 0.01	0.059 ± 0.003			0.038 ± 0.006		0.018 ± 0.003	0.028 ± 0.001
4-CF_3		0.042 ± 0.003						
3-CN		0.038 ± 0.003						
4-CN	0.049 ± 0.008	0.032 ± 0.003					0.012 ± 0.002	0.014 ± 0.002

[a] At 25 °C, ionic strength 1.0, and pH 7.0 in 20% CH_3CN–80% H_2O; units of min^{-1} for $1/Y_{int}$.

Table IV. Dependence of Y_{int}/Slope upon X and Z for Reduction of 2 by 1[a]

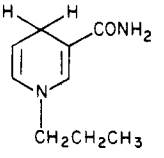
X	Z							
	4-CH_3	H	4-F	4-Br	3-F	4-CF_3	3-CN	4-CN
4-CH_3		240 ± 20						
H	93 ± 5	240 ± 10	290 ± 30	160 ± 10	410 ± 70	340 ± 70	1100 ± 200	>1000[b]
4-F		190 ± 30						
4-Br		220 ± 10						
3-F	50 ± 2	200 ± 10			550 ± 80		1800 ± 300	1000 ± 50
4-CF_3		200 ± 20						
3-CN		180 ± 20						
4-CN	160 ± 30	200 ± 20					1600 ± 300	1400 ± 200

[a] At 25 °C, ionic strength 1.0, and pH 7.0 in 20% CH_3CN–80% H_2O; units of M^{-1} for Y_{int}/slope. [b] k_{obsd} is independent of the concentration (≥1 mM) of 2 (Z = 4-CN).

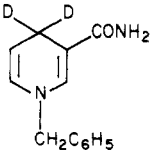
all 1-(substituted benzyl)-1,4-dihydronicotinamides (1) under conditions where 2 was in large excess. Substituent effects upon the slope and Y_{int} parameters for the double-reciprocal plots for these reactions are collected in Tables II–IV. From the data in these tables it is clear that, for any constant Z substituent, the $1/Y_{int}$ and 1/slope parameters show definite trends as the nature of the X substituent is varied, while the ratio Y_{int}/slope is essentially independent of X at constant Z. In fact, $1/Y_{int}$ and 1/slope (at constant Z) display excellent linear correlations with the Hammett σ constants for X. Hammett ρ_x values for these parameters are given in Table V for a number of Z substituents. Similar X-substituent dependences in the reduction of 7 by 1 are also apparent in Table I, and ρ_x values for this system are also included in Table V.

Examination of the data in Tables II–IV in terms of Z dependence at constant X indicates a somewhat more complicated situation than that described above at constant Z. The 1/slope parameters of Table II still show a simple dependence on the electronic effects of the Z substituents and can be expressed by Hammett correlations (Table V). On the other hand, $1/Y_{int}$ in Table III bears no simple correlation with the electronic properties of Z; for X = H, log $(1/Y_{int})$ vs. σ_z has a correlation coefficient 0.708. The ratio Y_{int}/slope (Table IV) shows a Z dependence which generally increases with the electron-withdrawing effect of Z, but in such an uneven manner that no simple correlation is apparent; for X = H, log (Y_{int}/slope) vs. σ_z has a correlation coefficient 0.800.

To allow further insight into the influence of the N-substituent in the 1,4-dihydronicotinamide upon the various kinetic parameters, we have also investigated the kinetics of reduction of both the *N*-methyl- and *N*-benzyl-5-nitroisoquinolinium cations by 1-propyl-1,4-dihydronicotinamide (9). These reactions also display ki-



9

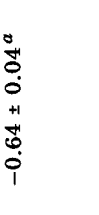
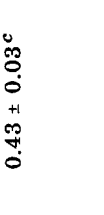


10

netic saturation for the pseudo-first-order rate constants. Data for these systems are presented in Table VI, which also includes a comparison of *N*-propyl and *N*-benzyl substituents on the 1,4-dihydronicotinamides for each isoquinolinium cation.

Kinetic isotope effects upon each kinetic parameter were also evaluated by using 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide (10) for the reduction of both the *N*-methyl- and *N*-benzyl-5-nitroisoquinolinium cations.

Table V. Hammett ρ_x and ρ_z Values for Reduction of 2 and 7 by 1

no.	reaction	ρ_x, $\rho(1/Y_{int})$	ρ_x, $\rho(1/slope)$	no.	reaction	ρ_x, $\rho(1/slope)$
1		−0.65 ± 0.02	−0.73 ± 0.05	5		−0.64 ± 0.04[a]
2		−0.67 ± 0.06	−0.78 ± 0.07	6		0.43 ± 0.03[c]
3			−0.072 ± 0.09[a]	7		0.54 ± 0.07[c]
4			−0.72[b]	8		0.57 ± 0.13[c]

[a] Based on 3 points only. [b] Based on 2 points only. [c] ρ_z.

Table VI. Reduction of 2 (Z = H) and 7 by 1 (X = H) and 9[a]

cation	reductant	1/slope	$1/Y_{int}$	Y_{int}/slope
2 (Z = H)	1 (X = H)	26 ± 1	0.108 ± 0.005	240 ± 10
	9	88 ± 9	2.0 ± 0.1	44 ± 2
ratio of	9/1	3.4 ± 0.5	19 ± 2	0.18 ± 0.02
7	1 (X = H)	7.1 ± 0.4	0.125 ± 0.006	57 ± 3
	9	33 ± 1	3.07 ± 0.01	10.8 ± 0.1
ratio of	9/1	4.6 ± 0.5	25 ± 2	0.19 ± 0.01

[a] At 25 °C, ionic strength 1.0, and pH 7 in 20% CH_3CN–80% H_2O. The units are as follows: 1/slope, M^{-1} min^{-1}; $1/Y_{int}$, min^{-1}; Y_{int}/slope, M^{-1}.

Table VII. Kinetic Isotope Effects for Reduction of 2 (Z = H) and 7 by 1 (X = H) and 10[a]

cation	reductant	1/slope	$1/Y_{int}$	Y_{int}/slope
2 (Z = H)	1 (X = H)	26 ± 1	0.108 ± 0.005	240 ± 10
	10	3.9 ± 0.2	0.026 ± 0.004	150 ± 20
ratio of	1/10	6.6 ± 0.7	4.2 ± 0.4	1.6 ± 0.3
7	1 (X = H)	7.1 ± 0.4	0.125 ± 0.006	57 ± 3
	10	1.3 ± 0.2	0.032 ± 0.003	42 ± 3
ratio of	1/10	5.5 ± 0.5	3.9 ± 0.4	1.4 ± 0.2

[a] At 25 °C, ionic strength 1.0, and pH 7.0 in 20% CH_3CN–80% H_2O. The units are as follows: 1/slope, M^{-1} min^{-1}; $1/Y_{int}$, min^{-1}; Y_{int}/slope, M^{-1}.

Table VIII. Kinetic Parameters for Eq 6 Derived from Schemes I-V

scheme	1/slope	$1/Y_{int}$	Y_{int}/slope
I	k_cK	k_c	K
II	k_2	k_2/K_{NP}	K_{NP}
III	k_cK	$k_c/(1 + K_{NP}/K)$	$K + K_{NP}$
IV	k_2	$k_2/(K_{NP} + K'_{NP})$	$K_{NP} + K'_{NP}$
V	k_cK	$k_cK/(K + K_{NP} + K'_{NP})$	$K + K_{NP} + K'_{NP}$

These data are collected in Table VII.

Discussion

The observation of kinetic saturation curves for the dependence of the pseudo-first-order rate constants on isoquinolinium cation concentration (Figure 2) suggests the formation of a complex between the isoquinolinium cation and the dihydronicotinamide. The linearity of the double-reciprocal plots in Figure 3 is consistent with a 1:1 complex being present in equilibrium with the reactants and with this equilibration being established rapidly relative to the rate of hydrogen transfer from the dihydronicotinamide to the isoquinolinium cation. However, any attempt to incorporate such a complexation preequilibrium into a reaction scheme immediately encounters a well-known conundrum; postulation of either a productive complex (Scheme I) or a nonproductive complex (Scheme

Scheme I

$$DHN + IQ^+ \overset{K}{\rightleftharpoons} C \xrightarrow{k_c} N^+ + DHIQ$$

Scheme II

$$DHN + IQ^+ \overset{K_{NP}}{\rightleftharpoons} C_{NP}$$

$$DHN + IQ^+ \xrightarrow{k_2} N^+ + DHIQ$$

II) leads to kinetically indistinguishable rate equations. Furthermore, Schemes I and II are also kinetically equivalent to Scheme III which includes both a productive

Scheme III

$$DHN + IQ^+ \overset{K_{NP}}{\rightleftharpoons} C_{NP}$$

$$DHN + IQ^+ \overset{K}{\rightleftharpoons} C \xrightarrow{k_c} N^+ + DHIQ$$

and a nonproductive complex. Under the pseudo-first-order kinetic conditions used in the current study, Schemes I–III each predict linear double-reciprocal equations of the form of eq 6, with the parameters being defined as in Table

$$\frac{1}{k_{obsd}} = \frac{\text{slope}}{[IQ^+]} + Y_{int} \qquad (6)$$

VIII. The various sets of experimental data reported in Tables I–IV will initially be considered in conjunction with each of these schemes.

Complex Formation. We note that all schemes predict that the ratio Y_{int}/slope represents the association constant for complex formation or the sum of the association constants if more than one complex is postulated (Table VIII). Thus the X-independent Y_{int}/slope ratios of Tables I and IV indicate that complex formation does *not* involve the X-benzyl group of the dihydronicotinamides (1). Irrespective of whether a productive or nonproductive complex is involved, the X-benzyl group must be essentially free in solution and not involved in an interaction of any consequence with the isoquinolinium cation. Complexation must occur via the interaction of all or part of the 1,4-dihydropyridine moiety of 1 with the isoquinolinium cation. This conclusion is further supported by the relatively small effect [about 5-fold (Table VI)] on Y_{int}/slope upon replacing the *N*-benzyl group of 1 by an *N*-propyl group. If complex formation involved solely π–π interaction via the aromatic ring of the *N*-benzyl group of 1, then such complexation should be destroyed upon introduction of a propyl group in place of the benzyl group.

The X independence of these association constants (i.e., $\rho \approx 0$) also clearly demonstrates that complexation does not result in any significant charge generation on the ring nitrogen atom of 1. Equilibrium constants for reactions in which charge is generated on the nitrogen atom of benzylamine derivatives are quite sensitive to the electronic effects of ring substituents in the benzyl group; e.g., ρ = 1.05 for benzylamine–benzylammonium cation equilibration,[13] and ρ = 0.95 for 1-benzyl-4-cyano-1,4-dihydronicotinamide–1-benzylnicotinamide cation equilibration.[10] Thus $\rho \approx 0$ for complex formation in the current reaction indicates that the dihydronicotinamide ring nitrogen atom in the complex is essentially electrically neutral and so clearly indicates that the kinetically detected complex is *not* a radical-cation species such as has sometimes been suggested[5,7,9] as an intermediate in the oxidation of 1,4-dihydronicotinamides.

Examination of the data in Table IV in terms of the Z dependence at constant X shows that Y_{int}/slope displays a general (but uneven) increase with the electron-withdrawing effect of Z. Thus the association constants of Table VIII are dependent on the Z substituent, although as noted above they are independent of X. This Z-dependence cannot be due to variation in electrical charge upon N-2 of 2 during complex formation since any such change in charge should be compensated for in the dihydronicotinamide and become apparent in an X dependence of Y_{int}/slope, which is contrary to the actual observations. The simplest explanation of the unusual Z dependences observed in Tables III and IV lies in the formation of a nonproductive complex via an interaction of the Z-benzyl substitutent of 2 with the dihydropyridine moiety of 1. In Scheme III, such a nonproductive complex is superimposed upon a reaction involving a productive complex. In the event that the X-independent complexes considered above are also nonproductive, the Z-dependent complexes represent a second class of nonproductive complex which are accounted for by C'_{NP} in Scheme IV.

Scheme IV

$$DHN + IQ^+ \overset{K_{NP}}{\rightleftharpoons} C_{NP}$$

$$DHN + IQ^+ \overset{K'_{NP}}{\rightleftharpoons} C'_{NP}$$

$$DHN + IQ^+ \xrightarrow{k_2} N^+ + DHIQ$$

Scheme V

$$DHN + IQ^+ \overset{K_{NP}}{\rightleftharpoons} C_{NP}$$

$$DHN + IQ^+ \overset{K'_{NP}}{\rightleftharpoons} C'_{NP}$$

$$DHN + IQ^+ \overset{K}{\rightleftharpoons} C \xrightarrow{k_c} N^+ + DHIQ$$

Scheme V results if a further nonproductive complex is incorporated into Scheme III. Schemes IV and V also generate eq 6 with parameters as listed in Table VIII. For Schemes III–V, the Y_{int}/slope ratios represent the sums of association constants, one of which is Z dependent and the other(s) Z independent. The difference (152 M^{-1}) in Y_{int}/slope for the *N*-methyl- (58 M^{-1}) and *N*-benzyl-5-nitroisoquinolinium cations (210 M^{-1}) is probably a reasonable estimate of the association constant for nonproductive complex formation via the *N*-benzyl group of the latter cation.

Two pieces of experimental evidence indicate that this Z-dependent C'_{NP} cannot involve an interaction via the X-benzyl group of 1. First, any complexation that involved interaction between the X-benzyl and Z-benzyl units would lead to an X-dependent Y_{int}/slope at constant Z, which is contrary to experimental observations. Second, the comparison of the *N*-propyl- and *N*-benzyldihydronicotinamides in Table VI indicates that the effect of replacing the benzyl substituent by a propyl group is independent of whether the 2-methyl- or 2-benzyl-5-nitroisoquinolinium cation is used as the hydride acceptor. Thus an interaction between the 1,4-dihydronicotinamide ring of 1 and the Z-benzyl group of 2 is indicated for C'_{NP}.

Substituent Effects upon Reaction Rate. For the reaction of various 1 with 7, Hammett ρ_x values of –0.65 and –0.73 are obtained for the X-substituent effects on $1/Y_{int}$ and 1/slope, respectively (Table V). These two ρ_x values are essentially the same in view of the experimental errors involved. This is consistent with $1/Y_{int}$ and 1/slope differing only by an association constant multiplier which is substituent independent within experimental error for both Schemes I and II (Table VIII). For the reaction of 1 with 2 (Z = H), $1/Y_{int}$ and 1/slope reveal ρ_x values of –0.67 and –0.78, respectively, which are again essentially identical within experimental error. Furthermore, ρ_x for reduction of 2 (Z = H) and 7 by 1 are identical, and so for a constant Z substituent, ρ_x for $1/Y_{int}$ and 1/slope are not influenced by nonproductive complex formation via the Z-benzyl group of 2. The similar ρ_x values for 1/slope for 2 (Z = 4-CH_3, 3-F, and 3-CN) in Table V, although based on fewer experimental points, confirm this Z independence of ρ_x.

(13) Blackwell, L. F.; Fischer, A.; Miller, I. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588.

For the reaction of 1 (X = H) with 2, $1/Y_{int}$ displays an essentially random variation with Z (Table III), while 1/slope is closely correlated with the σ constants for Z with $\rho_z = 0.43$. Similar ρ_z are obtained for 1 (X = 3-F) and 1 (X = 4-CN) (Table V), although these values are less accurate since they are based on data for fewer Z substituents. The reasons for a clean Hammett correlation with 1/slope but a random Z-dependence for $1/Y_{int}$ become clear upon examination of the definitions for these parameters in Table VIII for Schemes III–V in which complex formation via the Z-benzyl group was postulated above. In all cases, 1/slope represents either the second-order rate constant (k_2) for a bimolecular reaction, or, alternatively, the product (k_cK) of a first-order rate constant for intracomplex hydrogen transfer and an association constant which is independent of *both* X and Z. Thus, irrespective of whether the kinetically observed complexes are productive or nonproductive, substituent effects upon 1/slope in all cases represent substituent effects upon the rate constants for hydrogen transfer (i.e., upon k_2 or k_c). On the other hand, Schemes III–V predict that substituent effects upon $1/Y_{int}$ will be complicated by the influence of Z on both a rate constant and an association constant.

Since 1/slope is the only parameter which is a simple representation of the electronic effects of both X and Z upon the rates of the hydrogen transfer reaction, the Hammett ρ_x and ρ_z derived for 1/slope will be exclusively used in the detailed consideration of the nature of the rate-determining transition state in the following discussion.

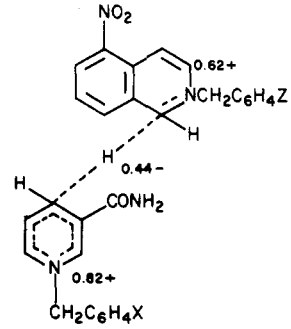
Nature of the Rate-Determining Transition State. Although they contain a small contribution from secondary isotope effects, the magnitudes of the 1/slope deuterium isotope effects in Table VII clearly indicate that these are predominately primary kinetic isotope effects and that carbon–hydrogen bond-breaking occurs during the rate-determining transition state for these hydrogen-transfer reactions. The ^1H NMR spectral studies presented above indicate that this hydrogen atom is transferred directly to the isoquinolinium cation without exchange with solvent protons.

Reactions 2 and 6 of Table V represent the most closely related and most extensive sets of experimental data on which a comparison of X and Z electronic effects can be based. Consequently, $\rho_x = -0.78$ and $\rho_z = 0.43$ will be used exclusively in the following considerations. All other ρ_x and ρ_z values in Table V are within experimental error of these two values.

For reaction 2, $\rho_x = -0.78$ clearly indicates that considerable positive charge is generated on the dihydronicotinamide in the rate-determining transition state. A quantitative estimate of the magnitude (δ) of positive charge generated in this transition state can be made from a comparison of $\rho_x = -0.78$ with the equilibrium ρ value of −0.95 for the dissociation of cyanide ion from **5** (chemical reverse of eq 2) which produces a unit positive charge on the nicotinamide cation product.[10] Thus, $\delta = 0.78/0.95 = +0.82$ represents the charge carried by the nicotinamide moiety in the transition state.

For reaction 6, $\rho_z = 0.43$ indicates a significant increase in electron density (i.e., decrease in positive charge) upon proceeding to the transition state from the reactant isoquinolinium cation. Using $\rho = 1.14$ for the equilibrium constant of the reaction in eq 3 as a reference point for the complete neutralization of one unit of positive charge,[11] we can estimate the fraction (ξ) of positive charge neutralized in the isoquinolinium cation upon going to the transition state as $\xi = 0.43/1.14 = 0.38$. Thus in the transition state the isoquinoline moiety bears 1 − 0.38 = 0.62 of a unit positive charge.

Our data therefore show[14] that in the rate-determining transition state for the reaction of eq 1, a charge of +0.82 has been generated on the dihydronicotinamide while only +0.38 of the initial +1 charge on the isoquinolinium cation has been neutralized. There is thus a discrepancy of 0.44 unit charge between the positive charge generated on the dihydronicotinamide and the positive charge neutralized on the isoquinolinium cation. To obtain a net charge balance, it is necessary that −0.44 charge should have been generated elsewhere in the transition-state species. The only obvious place that this negative charge can be located is on the hydrogen atom being transferred. Therefore, transition state 11 would seem to be most compatible with all of our experimental observations.



11

A hydrogen atom bearing a partial negative charge is obviously best described as being "hydridic" in character. Thus, transition state 11 represents a simple one-step transfer of a hydride ion from 1 to 2. The net increase in electron density on the hydrogen atom being transferred indicates that C–H bond-breaking at the hydride donor must be more advanced in the transition state than C–H bond-making on the acceptor.

The above calculations of the charge distribution in the transition state assume a linear relationship between ρ and electric charge. While such an assumption seems reasonable, there is no experimental test for such linearity. In the event that a nonlinear ρ vs. charge relationship were applicable, it would be expected to be represented by a monotonically increasing algebraic function of some type. A dramatic difference between such nonlinear functions in the nicotinamide and isoquinoline systems would be required to remove the discrepancy calculated above between the positive charge generated in the dihydronicotinamide and the positive charge neutralized on the isoquinolinium ion in the reaction transition state. There seems to be no reason to expect a dramatic difference in the ρ vs. charge relationships in these two species, since each involves a pyridine–dihydropyridine interconversion. Although a nonlinear ρ vs. charge relationship may influence the calculated magnitude of the fractional negative charge borne by the migrating hydrogen atom in the transition state, there seems to be no reason to doubt that this migrating hydrogen atom does bear some excess electron density and is thus "hydridic" in character.

Other Mechanistic Possibilities. While we feel that all of the current experimental data for the reaction of eq

(14) The reference ρ value of 1.14 for the equilibrium of eq 3 refers to aqueous solutions rather than to 20% acetonitrile–80% water which is the reaction medium of the current study. For this latter solvent, ρ = 0.88 (aqueous) for eq 2 becomes[10] $\rho = 0.95$. A similar small increase above $\rho = 1.14$ for eq 3 would be expected in the mixed solvent. Correction for this small solvent effect would even further enhance the discrepancy between δ and ξ calculated here.

1 are readily reconciled in terms of a one-step hydride transfer in either a bimolecular reaction or, alternatively, an intramolecular reaction within a productive 1:1 complex, it is also of interest to consider these data in terms of the alternative stepwise mechanisms which have sometimes been proposed[1-5] for reductions of suitable hydride acceptors by 1,4-dihydronicotinamides. In considering such mechanisms it is important to bear in mind that the observed primary kinetic isotope effects require that C–H bond-breaking should occur in the rate-determining transition state.

Our experimental results require a fractional negative charge on the migrating hydrogen atom in the transition state. This requirement seems to eliminate mechanisms in which the hydrogen atom migrates as a proton (e.g., $e^- + H^+ + e^-$). While a transition state for proton migration may carry only a small fractional positive charge on the migrating hydrogen atom, it is not reasonable to construe a migrating hydrogen atom that bears a significant fractional negative charge as being a migrating proton.

For mechanistic postulates in which hydrogen transfer occurs as a hydrogen atom [i.e., $H\cdot + e^-$ (a) or $e^- + H\cdot$ (b)], the deuterium kinetic isotope effects (Table VII) require that hydrogen atom migration should occur in the rate-determining step. For (a), the rate-determining step involves conversion of 1 into an electrically netural radical. While it is true that the ring nitrogen atom of the radical intermediate is electron deficient due to dipolar resonance contributions, it is difficult to imagine the dihydronicotinamide moiety as a whole bearing a significant positive charge during the neutral hydrogen atom transfer. Certainly a charge of +0.82 in this transition state seems very unlikely. For (b), rapid electron transfer is required to precede rate-determining hydrogen atom migration. This requirement means full positive charge on the nicotinamide moiety in the transition state, and a neutral isoquinoline moiety as a result of the initial rapid electron transfer. Even if a small fraction negative charge on the migrating hydrogen atom is allowed, the charge of +0.62 calculated for the isoquinoline moiety seems to be far too large to be attributed to such a mechanism.

Conclusion

In the present work we have shown that simultaneous studies on structure–reactivity correlations in both the hydride donor and hydride acceptor for the reduction of a series of 2-(Z-benzyl)-5-nitroisoquinolinium cations by a series of 1-(X-benzyl)-1,4-dihydronicotinamides have provided a method for gaining insight into mechanistic problems in hydride-transfer reactions when coupled with primary kinetic isotope effects. The results of the current study may be generalized as follows: if the increase in positive charge on the hydride donor in the transition state for a hydride transfer reaction is greater than the increase in negative charge (or decrease in positive charge) on the hydride acceptor, then negative charge must be borne by the migrating hydrogen species. A partially negatively charged hydrogen species is clearly "hydridic" in character, and we feel that such a mechanism is most simply referred to as a direct hydride transfer reaction.

Although the reaction of the current study can be most simply reconciled as a direct hydride transfer, the question of the generality of this mechanism in other 1,4-dihydronicotinamide reductions remains open but susceptible to testing by the current methods in many cases.

Experimental Section

Salts of the 2-(Z-benzyl)-5-nitroisoquinolinium cations (2) and 1-methyl-5-nitroisoquinolinium bromide were prepared and characterized as previously reported.[11,15] Potassium hydrogen phosphate, potassium chloride, potassium hydroxide, and acetonitrile (spectroscopic grade) were all the best commercially available grades.

Table IX. 1-(X-benzyl)-1,4-dihydronicotinamides (1)

X	mp, °C	^{1}H NMR,[a] δ	λ_{max},[b] nm
4-CH_3	87–88[c]	2.32 (3 H, s), 3.04 (2 H, m), 4.24 (2 H, s), 4.69 (1 H, m), 5,83 (1 H, d), 6.94 (2 H, s), 7.18 (4 H, s)	360
H	119–120[d]	3.05 (2 H, m), 4.30 (2 H, s), 4.71 (1 H, m), 5.84 (1 H, d), 6.95 (1 H, s), 7.33 (5 H, s)	357
4-F	106–107[e]	3.04 (2 H, m), 4.28 (2 H, s), 4.71 (1 H, m), 5.83 (1 H, d), 6.94 (1 H, s), 7.20 (4 H, m)	358
4-Br	56–57	3.04 (2 H, m), 4.27 (2 H, s), 4.72 (1 H, m), 5.81 (1 H, d), 6.93 (1 H, s), 7.37 (4 H, q)	360
3-F	66–68	3.13 (2 H, m), 4.27 (2 H, s), 4.70 (1 H, m), 5.67 (1 H, d), 7.07 (5 H, m)[f]	356
4-CF_3	80–81.5	3.06 (2 H, m), 4.39 (2 H, s), 4.74 (1 H, m), 5.83 (1 H), d), 6.96 (2 H, s), 7.58 (4 H, q)	357
3-CN	60–62	3.17 (2 H, m), 4.30 (2 H, s), 4.77 (1 H, m), 5.62 (1 H, d), 7.07 (1 H, s), 7.48 (4 H, m)[f]	360
4-CN	145.5–146[c]	3.06 (2 H, m), 4.38 (2 H, s), 4.74 (1 H, m), 5.82 (1 H, d), 6.92 (1 H, s), 7.58 (4 H, q)	358

[a] Unless indicated otherwise, all spectra are obtained in CD_3CN relative to tetramethylsilane. [b] In 20% CH_3CN–80% H_2O. [c] Compound reported in ref 8 without melting point data. [d] Lit.[16] 122 °C. [e] Lit.[18] 112–114.5 °C. [f] In $CDCl_3$ relative to tetramethylsilane.

1-(X-benzyl)nicotinamide (3) salts were prepared[10] by refluxing nicotinamide with an appropriate substituted benzyl bromide in acetone for 16–24 h. The salts were obtained as white, needlelike, crystals upon recrystallization from ethanol and were characterized by ^{1}H NMR spectroscopy.

1-(X-benzyl)-1,4-dihydronicotinamides (1) were prepared by adding the appropriate nicotinamide cation to a solution of sodium dithionite in aqueous sodium carbonate at 45–50 °C by the general method of Mauzerall and Westheimer.[16] The products precipitated as yellow solids and were recrystallized several times from 1:2 (v/v) ethanol–water. The physical properties of these compounds are reported in Table IX.

1-Propyl-1,4-dihydronicotinamide (9) was similarly prepared from 1-propylnicotinamide bromide.

1-Benzyl-4,4-dideuterio-1,4-dihydronicotinamide (10) was prepared by a series of reductions by sodium dithionite in D_2O followed by reoxidations to the nicotinamide cation by chloranil.[17] After three oxidations and four reductions in D_2O, the C-4 deuterium content was ≥99% as indicated by ^{1}H NMR and mass spectra.

Isolation of 1,2-Dihydroisoquinoline Products. 1,2-Dihydro-2-methyl-5-nitroisoquinoline (8) was prepared by mixing (a) 2.0 mL of a 0.1 M solution of 1-benzyl-1,4-dihydronicotinamide in acetonitrile, (b) 5.0 mL of a 0.04 M solution of 2-methyl-5-nitroisoquinolinium bromide in pH 7.0 phosphate buffer containing 2 M KCl, and (c) 3.0 mL of water to make a total reaction

(15) Bunting, J. W.; Kabir, S. H. J. Org. Chem. 1978, 43, 3662.
(16) Mauzerall, D.; Westheimer, F. W. J. Am. Chem. Soc. 1955, 77, 2261.
(17) Caughey, W. S.; Schellenberg, K. A. J. Org. Chem. 1966, 31, 1978.
(18) Dittmer, D. C.; Kolyer, J. M. J. Org. Chem. 1963, 28, 2288.

volume of 10 mL. The mixture was stirred for 1 h, and the dark red product was extracted into chloroform. After removal of chloroform on a rotary evaporator, a dark red solid was obtained. Spectral data of 8 were obtained (Results) immediately upon isolation, since this compound is quite sensitive to air oxidation to the 1-isoquinolinone. Upon evaporation to dryness of the aqueous layer from the above extraction, a solid was obtained which had a ^{1}H NMR spectrum in D_2O [δ 6.02 (2 H, s), 7.60 (5 H, s), 8.33 (1 H, quasi triplet), 9.02 (1 H, d), 9.18 (1 H, d), 9.45 (1 H, s)] identical with that of the 1-benzylnicotinamide cation.

Product isolation from the reduction of 7 by either 1-(4-cyanobenzyl)-1,4-dihydronicotinamide or 1-benzyl-4,4-dideuterio-1,4-dihydronicotinamide was done in a similar manner, except that 5- and 3-fold excesses, respectively, of the isoquinolinium salt were used to speed up the reaction.

Kinetic Studies. All rate data were obtained in 20% acetonitrile–80% water (v/v) at 25 °C, pH 7.0 (0.005 M phosphate buffer), and an ionic strength of 1.0 (KCl). The absorbance at 450 nm was recorded as a function of time with either a Unicam SP-1800 spectrophotometer equipped with a Unicam AR-25 linear recorder or with a Varian Cary 210 spectrophotometer. Reaction solutions contained the 1,4-dihydronicotinamide (0.08 mM) and appropriate concentrations of the isoquinolinium cation (1–50 mM) in a 10 mm path length cell.

Pseudo-first-order rate constants were evaluated from the slopes of Guggenheim plots over 2–4 reaction half-times after digitizing the absorbance vs. time curves by using the interactive digital plotter of a Tektronix 4051 computer.

Acknowledgment. This work was supported by the award of an Operating Grant to J.W.B. by the Natural Sciences and Engineering Research Council of Canada.

Registry No. 1 (X = 4-CH_3), 56133-29-0; 1 (X = H), 952-92-1; 1 (X = 4-F), 1893-57-8; 1 (X = 4-Br), 78186-16-0; 1 (X = 3-F), 78186-17-1; 1 (X = 4-CF_3), 78186-18-2; 1 (X = 3-CN), 78186-19-3; 1 (X = 4-CN), 56133-27-8; 2 (Z = 4-CH_3), 64840-46-6; 2 (Z = H), 52166-52-6; 2 (Z = 4-F), 78186-20-6; 2 (Z = 4-Br), 64840-44-4; 2 (Z = 3-F), 64840-45-5; 2 (Z = 4-CF_3), 78186-21-7; 2 (Z = 3-CN), 64840-43-3; 2 (Z = 4-CN), 64840-42-2; 3 (X = 4-CH_3), 78186-22-8; 3 (X = H), 16183-83-8; 3 (X = 4-F), 78186-23-9; 3 (X = 4-Br), 78186-24-0; 3 (X = 3-F), 78186-25-1; 3 (X = 4-CF_3), 78186-26-2; 3 (X = 3-CN), 78186-27-3; 3 (X = 4-CN), 78186-28-4; 7, 46271-32-3; 8, 69337-15-1; 9, 17750-24-2; 10, 60172-94-3; nicotinamide, 98-92-0; 4-methylbenzyl bromide, 104-81-4; benzyl bromide, 100-39-0; 4-fluorobenzyl bromide, 459-46-1; 4-bromobenzyl bromide, 589-15-1; 3-fluorobenzyl bromide, 456-41-7; 4-(trifluoromethyl)benzyl bromide, 402-49-3; 3-cyanobenzyl bromide, 28188-41-2; 4-cyanobenzyl bromide, 17201-43-3; 1-propylnicotinamide bromide, 52047-79-7.

Nature of Substituent Effects in Nuclear Magnetic Resonance Spectroscopy. 2. Factor Analysis of Carbon-13 Chemical Shifts in Unsaturated and Aromatic Halides[1]

William F. Bailey,*[2a] Eugene A. Cioffi,[2a] and Kenneth B. Wiberg*[2b]

Departments of Chemistry, The University of Connecticut, Storrs, Connecticut 06268, and Yale University, New Haven, Connecticut 06511

Received April 15, 1981

The effect of halogen substitution on the ^{13}C chemical shifts of a variety of unsaturated and aromatic systems has been studied via factor analysis. Two principal factors and one smaller factor were found to correlate all of the data to within ±0.42 ppm. The halogen parameters obtained in the analysis agree well with those previously observed for saturated halides. The origin of the chemical shifts is discussed and it is shown that the second halogen substituent factor is linearly related to a variety of physical properties of halogen-containing compounds.

Substituent effects on the carbon-13 chemical shifts of unsaturated and aromatic systems have received a great deal of attention in the 20 years that have elapsed since the pioneering work of Lauterbur[3] and Spiesecke and Schneider.[4] The interest in such systems is due in large measure to the results of early studies which suggested that ^{13}C shielding might be linearly related to local electron density. Although the situation is certainly more complex than once thought, the effect of substituents on the ^{13}C chemical shifts of aromatic and unsaturated molecules continues to attract the interest of numerous investigators.

The vast body of ^{13}C shift data available for π-electron-containing systems has been extensively reviewed[5-11] and critical discussions are available on the analysis of substituent induced shifts in terms of simple additivity schemes,[5-9] calculated charge densities,[5-13] linear free-energy relationships of the Hammett–Taft type,[13,14] dual substituent parameter schemes,[14-16] electric field effects,[17] and many other empirical and semiempirical models.[5-11] Recent progress toward the development of a unifying theoretical mode for nuclear shielding[9,18-20] holds the

(1) For the previous paper in this series, see: Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. *J. Org. Chem.* **1980**, *45*, 4936.
(2) (a) University of Connecticut. (b) Yale University.
(3) (a) Lauterbur, P. C. *Ann. N.Y. Acad. Sci.* **1958**, *70*, 841. (b) Lauterbur, P. C. *Tetrahedron Lett.* **1961**, 274.
(4) Spiesecke, H.; Schneider, W. G. *J. Chem. Phys.* **1961**, *35*, 731.
(5) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972.
(6) Levy, G. C.; Lichter, R. L.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Wiley-Interscience: New York, 1980.
(7) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: New York, 1976.
(8) Maciel, G. E. *Top. Carbon-13 NMR Spectrosc.* **1974**, *1*, 53.
(9) Martin, G. J.; Martin, M. L.; Odiof, S. *Org. Magn. Reson.* **1975**, *7*, 2.
(10) Ewing, D. F. *Org. Magn. Reson.* **1979**, *12*, 499.
(11) Hansen, P. E. *Org. Magn. Reson.* **1979**, *12*, 109.
(12) Henry, H.; Fliszar, S. *J. Am. Chem. Soc.* **1978**, *100*, 3312 and references therein.
(13) Nelson, G. L.; Williams, E. A. *Prog. Phys. Org. Chem.* **1976**, *12*, 229.
(14) Ewing, D. F. In "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978.
(15) Bromilow, J.; Brownlee, R. T. C.; Craik, D. J.; Sadek, M.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 2429 and references therein.
(16) Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1980**, *45*, 105 and 114.
(17) (a) Seidman, K.; Maciel, G. E. *J. Am. Chem. Soc.* **1977**, *99*, 3254. (b) Gschwendtner, W.; Schneider, H.-J. *J. Org. Chem.* **1980**, *45*, 3507.
(18) Ditchfield, R.; Ellis, P. D. *Top. Carbon-13 NMR Spectrosc.* **1974**, *1*, 1.
(19) Ebraheem, K. A.; Webb, G. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1977**, *11*, 149.

0022-3263/81/1946-4219$01.25/0