Kinetics of the Reduction of 3,4-Dihydroisoquinolinium Cations by 1,4-Dihydronicotinamides

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Pseudo-first-order rate constants for the reduction of the 2-methyl-3,4-dihydroisoquinolinium cation (1) by 1-(X-benzyl)-1,4-dihydronicotinamides (3) display kinetic saturation at high concentrations of 1 (20% CH_3CN–80% H_2O, 25 °C, ionic strength 1.0). Association constants for 1:1 complex formation are independent of X (1.4 ± 0.2 M^{-1}) and are most simply interpreted in terms of nonproductive complex formation. Pseudo-first-order rate constants for the reduction of 2-(Z-benzyl)-3,4-dihydroisoquinolinium cations (2) by 3 are linear for [2] up to approximately 60 mM. Hammett correlations for the second-order rate constants for these reactions give $\rho_x = -0.77$ for the reduction of 2 (Z = 4-CN) by 3 and $\rho_z = 0.83$ for the reduction of 2 by 3 (X = H). Comparisons of ρ_x and ρ_z with equilibrium ρ values for closely related reactions indicate that the migrating hydrogen atom bears a charge of −0.33 and thus is clearly hydridic in character. These results are closely analogous to the conclusions of our earlier study of the 1,4-dihydronicotinamide reduction of 5-nitroisoquinolinium cations which have similar pK_{R^+} values to those for 2. Thus similar reduction mechanisms apply to the reduction of aromatic and nonaromatic cations by 3. pK_{R^+} values for pseudobase formation from 2 are correlated with a Hammett $\rho = 1.72$. The second-order rate constant for hydroxide ion attack on 2 (X = H) is fivefold larger than for the 2-benzyl-5-nitroisoquinolinium cation, although the second-order rate constant for reduction by 3 (X = H) is 23-fold greater for the latter cation than for 2 (X = H). This is interpreted in terms of a poorer "fit" between 2 and 3 in the transition state for the reduction, relative to the better "fit" between the planar 5-nitroisoquinolinium cations and 3.

We have recently reported[1] on a detailed kinetic study of the reduction of 2-methyl- and 2-(substituted benzyl)-5-nitroisoquinolinium cations by 1-(substituted benzyl)-1,4-dihydronicotinamides. For these reactions, the kinetic Hammett ρ values for substituents in both the hydride donor and hydride acceptor species were compared with reference ρ values for equilibria which involve generation (or neutralization) of a unit positive charge in closely related systems. Such comparisons allow the description of the charge distribution on the hydride donor and hydride acceptor in the rate-determining transition state for hydrogen transfer. For the transition state of the above reaction, a difference was observed between the magnitude of the positive charge generated on the dihydronicotinamide moiety and the positive charge neutralized on the isoquinolinium cation. This discrepancy can be interpreted in terms of a significant fractional negative charge being borne by the migrating hydrogen atom, which must therefore be "hydridic" in character.

We now report a further application of this approach to a related reaction, namely, the reduction of 3,4-dihydroisoquinolinium cations by 1-(substituted benzyl)-1,4-dihydronicotinamides (eq 1). This reaction is of interest since it involves reduction in a nonaromatic ring of a hydride acceptor which is a close match to the corresponding 5-nitroisoquinolinium cation in terms of susceptibility toward nucleophilic attack as expressed by pK_{R^+} values for hydroxide ion addition. Steric and solvation effects in the vicinity of C-1 and N-2 should be quite similar in comparison of transition states for the reduction of 5-nitroisoquinolinium and 3,4-dihydroisoquinolinium cations. Thus any differences which are found for these two series of cations should be directly attributable to reduction occurring in a nonaromatic ring rather than in an aromatic ring.

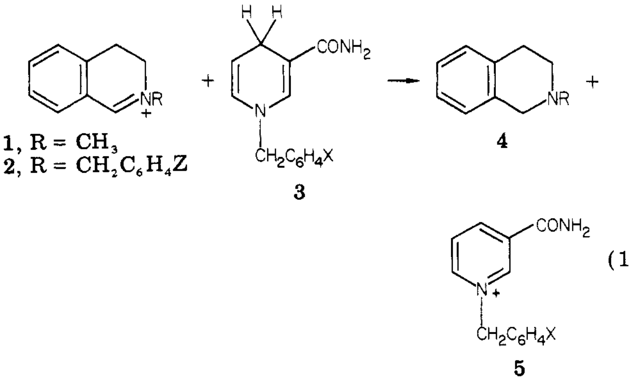

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Table I. Kinetic Parameters[a] for Reduction of 1 by 3

X	$10^3(1/\text{slope})$, M^{-1} s^{-1}	$10^3(1/Y_{int})$, s^{-1}	Y_{int}/slope, M^{-1}
H	3.3 ± 0.3	2.7 ± 0.3	1.2 ± 0.2
4-F	3.1 ± 0.3	2.4 ± 0.3	1.3 ± 0.2
4-Br	2.95 ± 0.3	1.9 ± 0.2	1.6 ± 0.2
3-F	2.15 ± 0.3	1.65 ± 0.2	1.3 ± 0.2
3-CN	1.5 ± 0.2	1.13 ± 0.1	1.3 ± 0.2
4-CN	1.4 ± 0.2	0.92 ± 0.08	1.5 ± 0.2

[a] Parameters for eq 2 in 20% CH_3CN–80% H_2O at 25 °C and an ionic strength of 1.0.

Results

Kinetic Studies. The disappearance of 3 in the presence of 400–5000-fold excesses of 1 was followed at 400 nm in 20% acetonitrile–80% water (v/v) at pH 7 (5 mM phosphate buffer), 25 °C, and an ionic strength of 1.0. All reaction rates were first-order in [3], and pseudo-first-order rate constants (k_{obsd}) were evaluated for the reaction of each of 3 (X = H, 4-F, 4-Br, 3-F, 3-CN, and 4-CN) with 1 over the concentration range [1] = 0.08–0.9 M. The dependence of k_{obsd} on [1] (Figure 1) displayed a kinetic saturation phenomenon with increasing concentrations of 1. Replots of these data in the form $1/k_{obsd}$ vs. $1/[1]$ were linear and could be described by eq 2. The parameters $1/Y_{int}$ and 1/slope were evaluated for each X in 3 and are collected in Table I.

$$1/k_{obsd} = Y_{int} + \text{slope}/[1] \qquad (2)$$

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[1] Bunting, J. W.; Sindhuatmadja, S. *J. Org. Chem.* 1981, *46*, 4211.

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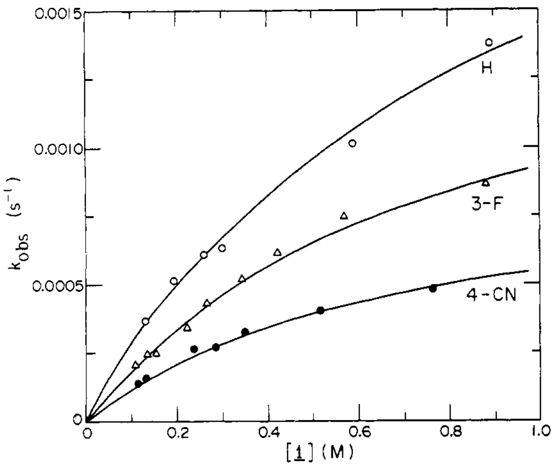


Figure 1. Pseudo-first-order rate constants for the reduction of 1 by 3 (X = H, 3-F, or 4-CN).

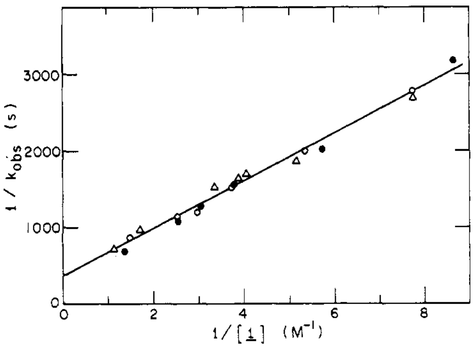


Figure 2. Reduction of 1 by 3 (X = H) at pH 7.0 at three phosphate buffer concentrations: △, 0.005 M; ○, 0.01 M; ●, 0.025 M.

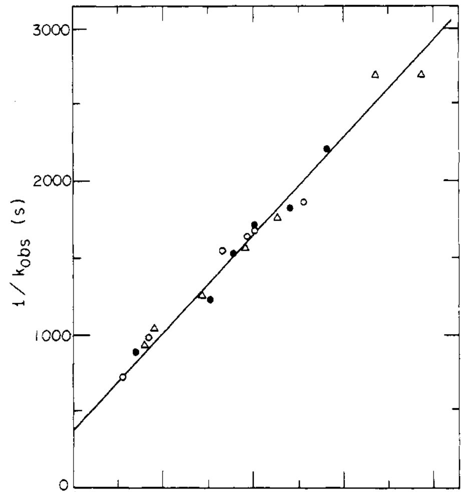
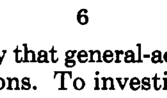


Figure 3. Reduction of 1 by 3 (X = H) at pH 6.5 (●), 7.0 (○), and 7.5 (△). All solutions contain total phosphate buffer at 0.005 M.

At pH 7.0, the reaction product 4 would be expected to be predominantly present as its conjugate acid 6. This



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suggests the possibility that general-acid catalysis may play a role in these reactions. To investigate this possibility,

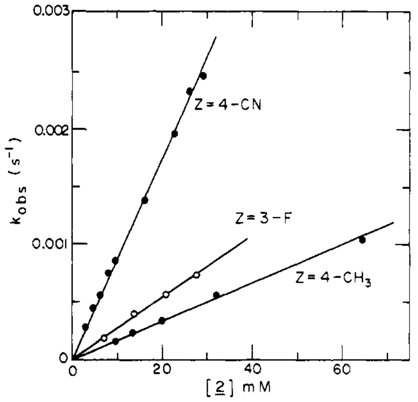


Figure 4. Pseudo-first-order rate constants for the reduction of 2 (Z = 4-CH_3, 3-F, and 4-CN) by 3 (X = H).

Table II. Second-Order Rate Constants for Reaction of 2 with 3[a]

X	Z	k_2, M^{-1} s^{-1}
H	4-CH_3	0.016 ± 0.002
H	H	0.019 ± 0.002 (0.0125 ± 0.0006)[b]
H	4-Br	0.027 ± 0.004
H	3-F	0.033 ± 0.004
H	3-CN	0.057 ± 0.003
H	4-CN	0.086 ± 0.001 (0.051 ± 0.001)[b]
4-CH_3	4-CN	0.110 ± 0.003
4-F	4-CN	0.074 ± 0.003
4-Br	4-CN	0.063 ± 0.002
3-F	4-CN	0.049 ± 0.003
3-CN	4-CN	0.029 ± 0.001
4-CN	4-CN	0.024 ± 0.001

[a] In 20% CH_3CN-80% H_2O at 25 °C and an ionic strength strength of 1.0. [b] For reduction using 1-benzyl-4-monodeuterio-1,4-dihydronicotinamide.

we have studied the reduction of 1 by 3 (X = H) at three phosphate buffer concentrations at pH 7.0 (Figure 2) and also at pH 6.5, 7.0, and 7.5 at a total phosphate buffer concentration of 0.005 M (Figure 3). In each of Figures 2 and 3 it is clear that the data for each of the three sets of experimental conditions fit the same correlation line. Furthermore, the correlation lines of Figures 2 and 3 are identical within experimental error: Figure 2, $Y_{int} = 370 \pm 40$, slope = 310 ± 10, $r = 0.994$; Figure 3, $Y_{int} = 400 \pm 40$, slope = 320 ± 10, $r = 0.989$. We therefore conclude that the reaction under study is not subject to general-acid or -base catalysis by phosphate buffer components, and k_{obsd} is pH independent in the pH region under study.

Rates of the reactions of 3 with the 2-(Z-benzyl)-3,4-dihydroisoquinolinium cations (2) were also studied by using large excesses of 2. These reactions were kinetically first-order in [3], and pseudo-first-order rate constants (k_{obsd}) were linear in [2] (Figure 4) over the concentration ranges that were amenable to study. Solubility considerations imposed maximum concentrations for 2 in the range 20–60 mM. Second-order rate constants calculated from the slopes of plots of k_{obsd} vs. [2] are listed in Table II for the reaction of 3 (X = H) as a function of the substituent Z in 2 and for 2 (Z = 4-CN) as a function of the substituent X in 3.

Similar studies of the reduction of 2 (Z = H) and 2 (Z = 4-CN) by the 4-monodeuterio derivative of 3 (X = H) gave the second-order rate constants indicated in Table II. If we ignore secondary isotope effects, the primary deuterium kinetic isotope effect can be calculated from $k^H/k^D = (k_2^{HH}/k_2^{HD})/(2 - (k_2^{HH}/k_2^{HD}))$, where k_2^{HH} and k_2^{HD} are the k_2 values of Table II for 3 and its 4-monodeuterio derivative, respectively. This calculation leads

Table III. pK_{R^+} Values for 3,4-Dihydroisoquinolinium[a] and 5-Nitroisoquinolinium Cations

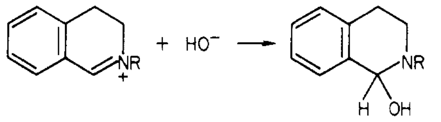
	pK_{R^+}	
N-alkyl	3,4-dihydroisoquinolinium	5-nitroisoquinolinium
CH_3	11.01 ± 0.07[b]	11.7[c]
$C_6H_5CH_2$	10.93 ± 0.04	11.29[d]
$4\text{-}BrC_6H_4CH_2$	10.25 ± 0.04	11.05[d]
$3\text{-}FC_6H_4CH_2$	10.21 ± 0.03	10.90[d]
$3\text{-}CNC_6H_4CH_2$	9.73 ± 0.03	10.60[d]
$4\text{-}CNC_6H_4CH_2$	9.74 ± 0.03	10.52[d]
$4\text{-}NO_2C_6H_4CH_2$	9.55 ± 0.03	10.40[d]

[a] At 25 °C and an ionic strength of 0.1. [b] Lit.[3] 10.75. [c] From ref 4. [d] From ref 5.

to $k^H/k^D = 3.2$ for **2** (Z = H) and 5.4 for **2** (Z = 4-CN) and clearly indicates that C–H bond breaking is involved in the rate-determining transition state for these reactions.

Spectral Characterization of Products. The reaction between **2** (Z = 4-CN) (20 mM) and **3** (X = H) (20 mM) was allowed to proceed overnight in 20% acetonitrile–80% D_2O. A few drops of concentrated DCl in D_2O were added to dissolve a small amount of precipitated product, and the ^1H NMR spectrum of the product solution was then determined. This spectrum contained signals for the 1-benzylnicotinamide cation (**5** (X = H)) at δ 9.37 (s, 1 H), 9.12 (d, 1 H), 8.96 (d, 1 H), 8.25 (dd, 1 H), 7.56 (s, 5 H), and 5.94 (s, 2 H), consistent with the spectrum of an authentic sample of this cation in the same solvent, and in addition contained signals at δ 7.85 (d, 2 H), 7.53 (s, 4 H), 7.33 (d, 2 H), 4.59 (s, 2 H), 4.39 (s, 2 H), and 3.25 (m, 4 H) which are readily assignable to the protons of the conjugate acid (**6** ($R = 4\text{-}CNC_6H_4CH_2$)) of the expected tetrahydroisoquinoline product (**4** ($R = 4\text{-}CNC_6H_4CH_2$)).

Pseudobase Formation by 3,4-Dihydroisoquinolinium Cations. 3,4-Dihydroisoquinolinium cations exhibit pH-dependent electronic absorption spectra in aqueous base as a result of the equilibration of these cations with their pseudobases (**7**, eq 3). From the pH dependence of their spectra, we have evaluated pK_{R^+} values for the cations **1** and **2** (Table III). For **2**, these pK_{R^+} values are correlated with the Hammett σ constants for the substituents Z by eq 4.



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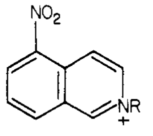
$$pK_{R^+} = (-1.72 \pm 0.14)\sigma + (10.83 \pm 0.07) \quad (r = 0.987) \tag{4}$$

For the 2-methyl-3,4-dihydroisoquinolinium cation (**1**), equilibration with its pseudobase occurs too rapidly at all pH values to allow measurement of equilibration rates by stopped-flow spectrophotometry. However, for the 2-benzyl-3,4-dihydroisoquinolinium cation (**2** (Z = H)), equilibration rates are accessible by this technique over the range pH 5.5–9.5. The pseudo-first-order rate constants (k) for equilibration are pH independent in this region (Figure 5). The pseudo-first-order rate constants (k_f) for pseudobase formation can be calculated[2] from eq 5, and values of k_f calculated in this way are proportional

$$k_f = k/(1 + [H^+]/K_{R^+}) \tag{5}$$

to $[^-OH]$ in the experimentally accessible pH range (slope = 1 in Figure 5). The second-order rate constant (k_{OH}) for hydroxide ion attack on the cation **2** (Z = H) is $(3.4 \pm 0.2) \times 10^5\ M^{-1}\ s^{-1}$ while the first-order rate constant (k_d) for pseudobase decomposition in this pH range is $k_d \approx k = 290 \pm 20\ s^{-1}$. The choice of 3,4-dihydroisoquinolinium cations for the current study was based upon the fact that they are known[3] to have pK_{R^+} values that are similar to the pK_{R^+} values of the 5-nitroisoquinolinium cations (**8**) of our earlier study.[1] The data of Table III indicate that the 3,4-dihydroisoquinolinium cations are all slightly more susceptible toward hydroxide ion addition than the corresponding 5-nitroisoquinolinium cations. This equilibrium observation is also paralleled by the relative rates of hydroxide ion attack upon these cations. Thus k_{OH} reported above for **2** (Z = H) is fivefold greater than $k_{OH} = 6.1 \times 10^4\ M^{-1}\ s^{-1}$ previously reported[5] for the 2-benzyl-5-nitroisoquinolinium cation.



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Discussion

The kinetic saturation effect observed in the reduction of **1** by **3** is similar to that observed previously[1,6] for the reduction of various isoquinolinium cations by **3**. The linearity of $1/k_{obsd}$ vs. $1/[\mathbf{1}]$ plots is consistent with the presence of a 1:1 complex between **1** and **3** which equilibrates with **1** and **3** much more rapidly than the hydrogen transfer between these species. Such a complex may be productive or nonproductive, and these two possibilities are kinetically equivalent. We have recently presented[6] kinetic data for the aromatic isoquinolinium systems that is most simply interpreted in terms of nonproductive complex formation, and a similar assumption will also be made in our initial consideration of the current data. Such nonproductive complex formation may be represented by Scheme I where DHN = 1,4-dihydronicotinamide, $DHIQ^+$ = 3,4-dihydroisoquinolinium cation, N^+ = nicotinamide cation, and THIQ = 1,2,3,4-tetrahydroisoquinoline. Under pseudo-first-order kinetic conditions ($[DHIQ^+] \gg [DHN]$), Scheme I generates the dependence of pseudo-first-order rate constant (k_{obsd}) on $[DHIQ^+]$ shown in eq 2 with 1/slope = k_2, $1/Y_{int} = k_2/K_{NP}$, and Y_{int}/slope = K_{NP}. If $[DHIQ^+] \ll 1/K_{NP}$, kinetic saturation is not observed, and k_{obsd} is linear in $[DHIQ^+]$. Under these conditions, which are found in the experimentally accessible concentration ranges for reactions of **3** with **2** (Figure 4), the observed second-order rate constant is equivalent to k_2 of Scheme I.

Scheme I

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

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

The Y_{int}/slope parameter of Table I represents K_{NP} of Scheme I. The magnitude of K_{NP} in Table I is similar to

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[2] Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1973**, *51*, 1965.

[3] Cook, M. J.; Katritzky, A. R.; Page, A. D.; Tack, R. D.; Witek, H. *Tetrahedron* **1976**, *32*, 1773.

[4] Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1974**, *52*, 962.

[5] Bunting, J. W.; Norris, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 1189.

[6] Bunting, J. W.; Chew, V. S. F.; Chu, G. *J. Org. Chem.*, previous paper in this issue.

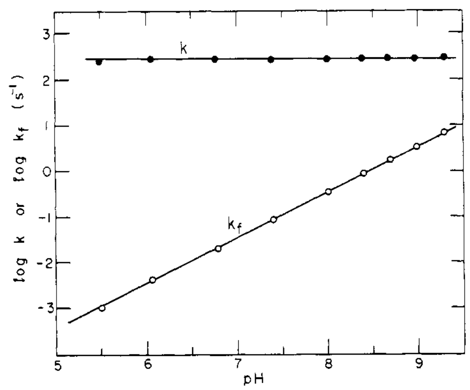
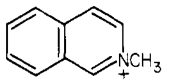


Figure 5. pH dependence of observed pseudo-first-order rate constants (k) for cation–pseudobase equilibration and pseudo-first-order rate constants (k_f) for pseudobase formation for **2** (Z = H).

that observed[6] in the reduction of the 2-methylisoquinolinium cation (**9**) (K_{NP} = 2.1 M^{-1}) and the 4-bromo-2-methylisoquinolinium cation (**10**) (K_{NP} = 1.5 M^{-1}) by **3** (X = H). Furthermore, K_{NP} for **1** in Table I appears to be independent of X in **3** which is similar to the previously observed[1] X independence of K_{NP} in the reduction of the 2-methyl-5-nitroisoquinolinium cation by **3**. These observations suggest that K_{NP} represents similar types of complexes in the interaction of **3** with 3,4-dihydroisoquinolinium cations and the aromatic isoquinolinium cations **8** (R = CH_3), **9**, and **10**. We have previously suggested[6] that the profound influence of the 5-nitro group of **8** upon K_{NP} suggests that complex formation predominantly involves the homocyclic ring of these isoquinolinium cations. The similarity of K_{NP} for **1** and **9** and **10** supports this interpretation since it seems unlikely that complexation would be equally effective with the pyridinium ring of **9** or **10** and with the dihydropyridinium ring of **1**. This point is considered in more detail in later discussion.



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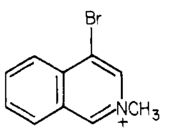

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The dependence of k_2 upon the substituent X in **3** for the reduction of **1** (k_2 = 1/slope of Table I) and for the reduction of **2** (Z = 4-CN) (Table II) may be expressed by the Hammett correlation equations [eq 6 for **1** and eq 7

$$\log k_2(\mathbf{1}) = (-0.58 \pm 0.08)\sigma_x - (2.45 \pm 0.03) \quad (r = 0.965) \qquad (6)$$

$$\log k_2(\mathbf{2}\ (Z = 4\text{-CN})) = (-0.77 \pm 0.05)\sigma_x - (1.07 \pm 0.02) \quad (r = 0.987) \qquad (7)$$

for **2** (Z = 4-CN)]. Since K_{NP} appears to be independent of X (average K_{NP} = 1.4 ± 0.2 M^{-1} in Table I), the dependence of k_2 upon σ_x can also be evaluated for **1** from $1/Y_{int} = k_2/K_{NP}$ of Table I. This treatment leads to eq 8. Statistical considerations give a clear preference for

$$\log k_2(\mathbf{1}) = (-0.67 \pm 0.04)\sigma_x - (2.41 \pm 0.02) \quad (r = 0.994) \qquad (8)$$

eq 8 over eq 6 as the best representation of the X-dependence of k_2 for reduction of **1** by **3**. The ρ_x values of eq 7 and 8 are quite similar and reflect similar charge neutralization in the transition state for the reduction of **1** and **2**. A similar observation was previously made[1] in the reduction of 5-nitroisoquinolinium cations (**8**).

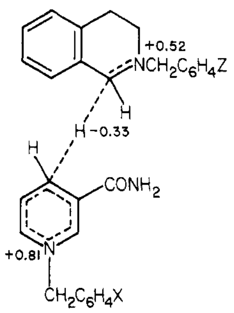
The ρ_x = −0.77 of eq 7 may be compared with ρ_x = −0.95 for the equilibrium constants for cyanide ion dissociation from 1-(X-benzyl)-4-cyano-1,4-dihydronicotinamides to generate the corresponding 1-(X-benzyl)-nicotinamide cations.[7] This ρ_x = −0.95 indicates the X-substituent sensitivity for an increase of the electrical charge upon the nicotinamide moiety from 0 to +1. Thus the partial charge (+δ) produced upon the nicotinamide moiety in the transition state for the reduction of **2** (Z = 4-CN) by **3** can be estimated from δ = 0.77/0.95 = +0.81.

The dependence of k_2 upon Z for the reduction of **2** by 1-benzyl-1,4-dihydronicotinamide (**3** (X = H), Table II) can be expressed by the Hammett correlation of eq 9.

$$\log k_2 = (0.83 \pm 0.10)\sigma_z - (1.71 \pm 0.04) \quad (r = 0.971) \qquad (9)$$

Equation 4 indicates that ρ_z = 1.72 for the equilibrium constants for the reaction of eq 3 in which complete charge neutralization occurs in the 2-benzyl-3,4-dihydroisoquinolinium cations **2**. Comparison of ρ_z = 0.83 in eq 9 with ρ_z = 1.72 for complete charge neutralization allows an estimate of the extent of charge neutralization experienced by **2** in the transition state for reduction of **2** by **3**. Thus ξ = 0.83/1.72 = 0.48 indicates that in the transition state for reduction the isoquinolinium moiety bears 1 − 0.48 = 0.52 of a unit positive charge.

The above estimates indicate a discrepancy between the charge generated on the nicotinamide moiety (δ = 0.81) in the transition state for reduction and the extent of charge neutralization (ξ = 0.48) on the 3,4-dihydroisoquinolinium cation in this transition state. Electrical neutrality requires the location of a net charge of −(0.81 − 0.48) = −0.33 elsewhere in the transition-state species. As indicated in an earlier study,[1,8] such a discrepancy is only readily rationalized in terms of a charge of −0.33 being borne by the migrating hydrogen atom which is thus "hydridic" in character (transition state **11**).



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The 3,4-dihydroisoquinolinium cations were chosen for the current study because they display pK_{R^+} values for hydroxide ion addition that are close to the pK_{R^+} values for the 5-nitroisoquinolinium cations which were the subjects of an earlier investigation.[1] The comparison of the reactivities of aromatic and nonaromatic cations toward reduction by 1,4-dihydronicotinamides is of inherent interest, and furthermore, these systems are sufficiently different that they allow a reasonably stringent test of the generality of our earlier conclusion[1] that in such reductions the hydrogen atom that undergoes transfer is "hydridic" in character. The X-benzyl and Z-benzyl substituent effects upon reaction rates in the current study closely parallel the analogous substituent effects observed in the reduction of 5-nitroisoquinolinium cations.[1] The charge distribution in the transition state **11** is very similar to that

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(7) Bunting, J. W.; Sindhuatmadja, S. *J. Org. Chem.* **1980**, *45*, 5411.

(8) This earlier work[1] also considers the limitations and assumptions that are inherent in this treatment.

deduced for the analogous transition state for 5-nitroisoquinolinium cation reduction, namely, +0.82 on nicotinamide, −0.44 on migrating hydrogen and +0.62 on isoquinoline. We feel that the similarity of these results in aromatic and nonaromatic ring systems, which were chosen for their similar susceptibilities to nucleophilic attack, provides strong support for our general conclusions that these reactions occur via single-step hydride-transfer mechanisms.

A potential inconsistency with the above interpretation appears if one compares the relative reactivities of 3,4-dihydroisoquinolinium cations and 5-nitroisoquinolinium cations in reactions wth hydroxide ion and in reductions with 1-benzyl-1,4-dihydronicotinamide. As noted above, the second-order rate constant, k_{OH}, for hydroxide ion attack upon the 2-benzyl-3,4-dihydroisoquinolinium cation is five-fold greater than k_{OH} for the 2-benzyl-5-nitroisoquinolinium cation. However, for reduction of these two cations by 1-benzyl-1,4-dihydronicotinamide, k_2 is 23-fold larger for the 5-nitroisoquinolinium cation than for the 3,4-dihydroisoquinolinium cation. For the *N*-methyl cations the relative k_2 values show a 36-fold ratio in favor of the 5-nitroisoquinolinium cation. Furthermore, in reductions with 1-benzyl-1,4-dihydronicotinamide, k_2 for **1** (3.3×10^{-3} M^{-1} s^{-1}) is only four-fold greater than for **9** (8×10^{-4} M^{-1} s^{-1})[6] although this latter cation is much less susceptible to hydroxide ion addition ($\Delta pK_{R^+} = 16.29 - 11.01 = 5.28$). These observations indicate that, in reductions with 1,4-dihydronicotinamides, 3,4-dihydroisoquinolinium cations display a lower reactivity relative to the corresponding aromatic isoquinolinium cation than expected on the basis of the relative reactivities of these two classes of cations with hydroxide ions. Superficially, this observation could be interpreted in terms of these reductions proceeding via a mechanism that does not involve nucleophilic attacks on these heterocyclic cations. However, as indicated above, there is now a considerable body of evidence from both the current and earlier studies which is most readily rationalized in terms of direct hydride transfer from the 1,4-dihydronicotinamide to the heterocyclic cation. We feel that the lower reactivity of 3,4-dihydroisoquinolinium cations relative to isoquinolinium cations in these reductions can best be accounted for in terms of steric interactions between the heterocyclic cation and the 1,4-dihydronicotinamide in either the transition state for hydride transfer in a bimolecular reaction or, alternatively, in the formation of a 1:1 molecular complex between the reactants prior to an intramolecular hydride transfer. The planar pyridinium ring of an aromatic isoquinolinium cation clearly places fewer geometric and other steric restraints upon complex formation than does the nonplanar dihydropyridinium ring of the 3,4-dihydroisoquinolinium cation. Consequently a better "fit" can be expected between 1,4-dihydronicotinamide and isoquinolinium cations than between 1,4-dihydronicotinamide and 3,4-dihydroisoquinolinium cations in either a bimolecular transition state or in a preformed productive 1:1 complex. In either mechanism, the poorer "fit" in the case of the 3,4-dihydroisoquinolinium cation effectively raises the activation energy for hydride transfer relative to the corresponding isoquinolinium cations and consequently reduces the reactivity of the 3,4-dihydroisoquinolinium cations in these reductions relative to what is expected on the basis of reactions with simple nucleophiles such as hydroxide ions.

For a bimolecular transition state these relative reactivities are expressed in k_2 of Scheme I above. For productive 1:1 complex formation Scheme I must be expanded as in Scheme II which gives the following parameters for eq 2: $1/\text{slope} = k_cK$; $1/Y_{int} = k_c/(1 + K_{NP}/K) \approx k_cK/K_{NP}$ for $K \ll K_{NP}$; $Y_{int}/\text{slope} = K + K_{NP} \approx K_{NP}$ for $K \ll K_{NP}$. For Scheme II we expect that k_c will reflect the inherent reactivity of the heterocyclic cation to nucleophilic attack as may be seen in k_{OH}, while K will be very dependent upon steric fit between the two species in the formation of productive complex C. Clearly, a poor fit will lead to a small association constant K, and variations in K may become the predominant determining factor for the magnitude of the experimentally observed second-order rate constant ($=k_cK$). It should also be noted that for $K \ll K_{NP}$, the experimentally determined association constant is K_{NP}, which is consistent with our above suggestions that nonproductive complex formation is being predominantly observed in the Y_{int}/slope experimental parameter.

Scheme II

$$\mathrm{DHN} + \mathrm{DHIQ}^+ \overset{K_{NP}}{\rightleftharpoons} \mathrm{C}_{NP}$$

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

Experimental Section

1-(X-benzyl)-1,4-dihydronicotinamides were prepared and characterized as described previously.[1] 3,4-Dihydroisoquinoline was purchased from Chemservice Co., Fairfield, NJ.

2-Methyl-3,4-dihydroisoquinolinium (1) iodide was prepared by stirring 3,4-dihydroisoquinoline with excess methyl iodide in acetone at room temperature. The yellow product was filtered off, washed, and dried; mp 127–128 °C (lit.[3] mp 126.5–128.5 °C).

2-(Z-benzyl)-3,4-dihydroisoquinolinium (2) bromides were prepared by stirring 3,4-dihydroisoquinoline with the appropriate ring-substituted benzyl bromide in acetone at room temperature. The precipitated products were recrystallized and characterized by ^{1}H NMR spectra and elemental analyses.

Kinetic Studies. 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 + heterocyclic cation salt). Variations on these conditions are noted in Figures 2 and 3. Absorbances of solutions were recorded as a function of time at a convenient wavelength on either a Unicam SP-1800 spectrophotometer equipped with a Unicam AR-125 linear recorder or alternatively on a Varian Cary 210 spectrophotometer. All reactions were under pseudo-first-order conditions with the absorbance due to the 1,4-dihydronicotinamide (0.1 mM) being followed at a convenient wavelength in the region 360–400 nm. Rate constants were obtained by fitting absorbance vs. time data directly to first-order kinetic equations or via the Guggenheim method for the slower reactions. In all cases, reactions were kinetically first order for at least 3 half-times.

pK_{R^+} values were determined spectrophotometrically in buffered aqueous solutions of ionic strength 0.1 by the general method of Albert and Serjeant.[9] Rates of cation–pseudobase equilibration were measured on a Durrum-Gibson stopped-flow spectrophotometer by mixing solutions of the pseudobase with appropriate buffers (final ionic strength = 0.1) at 25 °C. Absorbance vs. time curves were digitized (118 data points), and the data were fitted to first-order rate equations with a Tektronix 4051 minicomputer.

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Registry No. 1 (R = Me), 33718-23-9; 2 (Z = 4-Me), 81246-17-5; 2 (Z = H), 38602-73-2; 2 (Z = 4-Br), 81246-18-6; 2 (Z = 3-F), 81246-19-7; 2 (Z = 3-CN), 81246-20-0; 2 (Z = 4-CN), 81246-21-1; 2 (Z = 4-NO$_2$), 52166-49-1; 3 (X = H), 952-92-1; 3 (X = 4-F), 1893-57-8; 3 (X = 4-Br), 78186-16-0; 3 (X = 3-F), 78186-17-1; 3 (X = 3-CN), 78186-19-3; 3 (X = 4-CN), 56133-27-8; 3 (X = 4-Me), 56133-29-0.

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