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Relative Reactivities of Heteroaromatic Cations towards Reduction by 1,4-Dihydronicotinamides

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ABSTRACT

Kinetic data are reported for the equilibration of the 1-methyl-3-nitropyridinium cation with its pseudobase (hydroxide adduct) and for the reduction of this cation by 1-benzyl-1,4-dihydronicotinamide. The C-2 hydroxide adduct is the kinetically controlled product ($pK_{R+} = 11.6$) when this pyridinium cation is mixed with aqueous base, however, this species rearranges to the C-4 adduct as the thermodynamically more stable product ($pK_{R+} = 9.42$). The pH-dependence of this equilibration may be analyzed to give $k_{OH} = 1600\ M^{-1}s^{-1}$ for hydroxide ion attack at C-4 of this cation. Reduction of this pyridinium cation by 1-benzyl-1,4-dihydronicotinamide appears to occur exclusively at C-4 with second-order rate constant $k_2 = 0.72\ M^{-1}s^{-1}$ and $k_2^H/k_2^D = 2.0$ in 20% CH_3CN - 80% H_2O, ionic strength 1.0, 25°C.

The reactivities of pyridinium, quinolinium, isoquinolinium, acridinium and phenanthridinium cations of $pK_{R+} = 10.0$ towards both hydroxide ion and 1-benzyl-1,4-dihydronicotinamide are evaluated. Relative reactivities (k_2/k_{OH}) for these two processes are shown to be acridinium : quinolinium (C-4) : pyridinium (C-4) : quinolinium (C-2) : isoquinolinium : phenanthridinium = 1.6×10^5 : 3400 : 80 : <4 : 1.0 : 0.7 for predominantly aqueous reaction media. These data support the hypothesis that formation of 1,2-dihydropyridine systems upon reduction of heteroaromatic cations by 1,4-dihydronicotinamides occurs via direct one step hydride transfer, while formation of 1,4-dihydropyridines in such processes occurs preferentially by a mechanistically more complex process involving electron transfer.

There have been many recent investigations of the kinetics and mechanism of the reduction of various nitrogen heteroaromatic cations by 1,4-dihydronicotinamides. Since the original observations of Sigman et al.[1] in 1973, the reduction of acridinium cations has attracted many workers[2-13]. In addition, quantitative data on the rates of reduction of quinolinium[14], isoquinolinium[15,16] and phenanthridinium[10] cations are also now available. We have recently reported upon the kinetics of the reduction of nicotinonitrile cations by 1-benzyl-1,4-dihydronicotinamide[17], and have now obtained data, which we report below, for the reduction of the 1-methyl-3-nitropyridinium cation.

Extensive investigations of the rates and equilibria for hydroxide ion addition (i.e. pseudobase formation) to these various classes of heteroaromatic cations have also become available recently[18,19]. Thus relative reactivities of many heteroaromatic cations towards both hydroxide ion addition and 1,4-dihydronicotinamide reduction can now be calculated. Many of these reductions are believed to occur mechanistically via a one step hydride transfer from the hydride donor to the hydride acceptor[10,11,15,20-22]. In several cases, experimental and theoretical considerations point to the migrating hydrogen species bearing significant excess electron density in the rate-determining transition state and thus to be quite "hydridic" in character[15,20,21,23]. For such nucleophilic reductions one would predict that the relative reactivities towards hydroxide ion addition and 1,4-dihydronicotinamide reduction would be closely parallel upon variation of the heteroaromatic cation substrate.

The use of pseudobase formation as a model for hydride transfer to heteroaromatic cations has been investigated by Kreevoy and Lee[21]. They report that for a limited set of quinolinium cations there is a close correlation between the equilibrium constants for pseudobase formation and the equilibrium constants for hydride transfer from 9,10-dihydro-10-methylacridine. However, this correlation seems to break down for a more diverse set of dihydro heterocycles reacting with the 10-methylacridinium cation[36]. As discussed in detail below, we feel that these correlations (or lack thereof) may be strongly influenced by solvation effects in the aqueous alcoholic solvent system employed in these studies.

Bernasconi[24] has stressed that care should be taken to make comparisons of relative reactivities that are not contaminated by thermodynamic influences. Thus, considerations of relative reactivities of different classes of heteroaromatic cations towards either hydroxide ion addition or 1,4-dihydronicotinamide reduction should only be made for reactions having similar equilibrium constants. The availability of extensive linear free energy relationships for many of these two reaction classes allows interpolation and extrapolation to members of a particular class even though such members may not be directly accessible. Sufficient experimental data are now available to allow such a detailed comparison of relative reactivities for pyridinium, quinolinium, isoquinolinium, acridinium and phenanthridinium cations. We present such a comparison in the current work, and suggest that future considerations of the mechanisms of these 1,4-dihydronicotinamide reductions should take these observed relative reactivities into consideration.

EXPERIMENTAL DETAILS

3-Nitropyridine was prepared from 2-chloro-3-nitropyridine (Aldrich Chemical Co.) as described by Barlin[25]. 1-Benzyl-1,4-dihydronicotinamide and its 4,4-dideuterio derivative were prepared and characterized as previously described[15].

1-Methyl-3-nitropyridinium bromide

3-Nitropyridine (400 mg) was stirred with methyl bromide (3 ml) in acetone solution (10 ml) in a pressure bottle until precipitation of the product was complete. The bromide salt was recrystallized several times from ethanol. Pmr spectrum (in CF_3CO_2H): δ 4.80 (s, 3H), 8.67 (m, 1H), 9.42 (m, 1H), 9.80 (d, 1H).

Kinetic Studies

The reduction of the 1-methyl-3-nitropyridinium cation by 1-benzyl-1,4-dihydronicotinamide was studied in 20% CH_3CN - 80% H_2O, pH 7.0 (5 mM phosphate buffer), ionic strength 1.0 (KCl) at 25°C. All kinetic runs were initiated by the addition of a solution of the dihydronicotinamide in acetonitrile to a temperature equilibrated solution of the 1-methyl-3-nitropyridinium cation in aqueous buffer. Under the current reaction conditions, the hydration of the C(5)-C(6) double bond of the dihydronicotinamide is extremely slow[13], and cannot compete effectively with the more rapid hydride transfer reaction.

The formation of 1,4-dihydro-1-methyl-3-nitropyridine was monitored by the increase in absorbance at 400 nm on a Varian Cary 219 spectrophotometer in reactions of the 1-benzyl-1,4-dihydronicotinamide (0.1 mM) with large excesses of the 1-methyl-3-nitropyridinium cation (1.0 - 5.0 mM). All reactions proved to be kinetically pseudo-first-order in the reducing reagent, with the observed pseudo-first-order rate constant being proportional to the concentration of the 1-methyl-3-nitropyridinium cation.

The rates of equilibration of the 3-nitropyridinium cation and its pseudobases were measured on the Durrum-Gibson stopped-flow spectrophotometer in aqueous solutions (pH 10 - 13) at ionic strength 0.1 and 25°C. Buffer solutions were either sodium bicarbonate - sodium carbonate mixtures or standard potassium hydroxide solutions containing sufficient potassium chloride to give ionic strength 0.1 after mixing in the stopped-flow spectrophotometer. The pK_{R+} value of the thermodynamically stable pseudobase of the 1-methyl-3-nitropyridinium cation was evaluated by the spectrophotometric method of Albert and Serjeant[26] in the pH range 8.5 - 10.5 using borate and carbonate buffer solutions at ionic strength 0.1 and 25°C.

RESULTS

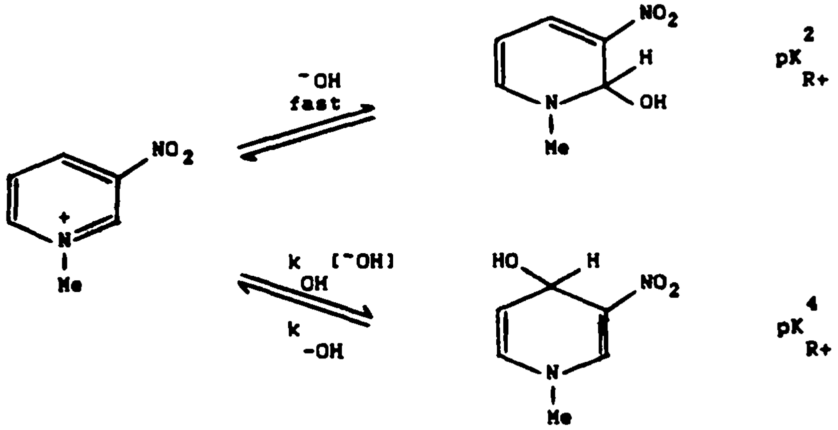
Pseudobase formation by the 1-methyl-3-nitropyridinium cation

The electronic absorption spectrum of this cation in aqueous solution displays a pH-dependence consistent with its equilibration with its pseudobase with $pK_{R+} = 9.42 \pm 0.02$ (ionic strength 0.1, 25°C). This pseudobase displays λ_{max} 400 nm (extinction coefficient $2.0 \times 10^4\ M^{-1}cm^{-1}$) measured at pH 12.0, and is typical of the spectra displayed by 1,4-dihydro-3-nitropyridines[27]. The spectra of these equilibrated solutions contain no significant absorption in the vicinity of 500 nm.

When neutral aqueous solutions of the 1-methyl-3-nitropyridinium cation are mixed with aqueous buffers (pH 10 - 13) in the stopped-flow spectrophotometer, a transient species with absorption maximum in the vicinity of 520 nm is observed. The formation of this species is complete in times similar to the mixing dead-time in our instrument in most cases. In all cases studied, the formation of this transient is complete in less than 10 milliseconds in this pH range. This transient absorption at 520 nm subsequently decays to close to zero absorbance at this wavelength at rates which are conveniently monitored on the stopped-flow system. This decay proved to be kinetically first-order in the pyridine species, with pseudo-first-order rate constants (k_{obs}) that are almost pH-independent in the range pH 10 - 13. Thus, after a twofold increase between pH 10 and 11, $k_{obs} = 6.5 \pm 0.4\ sec^{-1}$ in the range pH 11 - 13. The maximum intensity of the absorbance at 520 nm is pH-dependent, being quite small at pH 10 and increasing to a constant value equivalent to an extinction coefficient of $1.2 \times 10^4\ M^{-1}cm^{-1}$ at pH 13. The pH-dependence of the maximum absorbance is typical of that of the equilibration of an acid with its conjugate base, and allows the evaluation of a $pK_a = 11.6 \pm 0.1$ for this transient species (ionic strength 0.1, 25°C).

The kinetic features presented above for cation - pseudobase equilibration for the 1-methyl-3-nitropyridinium cation are very similar to those described previously for C-3 substituted 1-methylquinolinium cations[19,28]. For quinolinium cations bearing an electron-withdrawing C-3 substituent, it has been clearly demonstrated that although kinetic control of pseudobase formation favors the C-2 hydroxide adduct, the thermodynamically more stable pseudobase is the C-4 adduct. The stopped-flow spectrophotometric observations reported in the current study are consistent with a similar kinetically controlled pseudobase formation by hydroxide ion attack at C-2 of the 1-methyl-3-nitropyridinium cation, to give a species having an absorption maximum in the vicinity of 500 nm. Such an absorption maximum is known to be characteristic of 1,2-dihydro-3-nitropyridine derivatives[27]. Subsequent isomerization to a thermodynamically more stable C-4 hydroxide adduct having a shorter wavelength absorption maximum then occurs. This situation is detailed in Scheme 1, and we can identify $pK^2_{R+} = 11.6$ and $pK^4_{R+} = pK^E_{R+} = 9.42$ respectively. These data allow the evaluation[19] of the equilibrium ratio of pseudobases as 150:1 in favor of the C-4 over the C-2 pseudobase species. This ratio is essentially identical to that previously reported (i.e. 180:1) for the C-4 and C-2 hydroxide adducts of the 1-methyl-3-nitroquinolinium cation[19,28].

SCHEME 1



The pH-dependence described above for the pseudo-first-order rate constants (k_{obs}) for the isomerization of the C-2 to the C-4 hydroxide adduct is also similar to that reported for this process in the quinolinium cations[19,28]. The pH-independent $k_{obs} = 6.5\ s^{-1}$ for pH 11 - 13 is related to k_{OH} of Scheme 1 by $k_{obs} = k_{OH}\ K_w\ /\ K^2_{R+}$ where K_w is the ionic product of water. Thus, $k_{OH} = 1600\ M^{-1}s^{-1}$ is the second-order rate constant for hydroxide ion attack at C-4 of the 1-methyl-3-nitropyridinium cation, and $k_{-OH} = 0.042\ s^{-1}$ for the spontaneous ejection of hydroxide ion from the C-4 pseudobase.

Reduction of the 1-methyl-3-nitropyridinium cation

The time dependence of the electronic absorption spectrum of a solution containing an equimolar mixture of 1-benzyl-1,4-dihydronicotinamide and the 1-methyl-3-nitropyridinium cation is shown in Figure 1. The absorption maximum at 358 nm due to the 1,4-dihydronicotinamide decreases with time in favor of a new absorption maximum at 438 nm. The clean isosbestic point at 385 nm indicates that no significant concentration of any intermediate species is produced during the course of this reaction. The product spectrum is consistent with the spectrum reported for an authentic sample of 1,4-dihydro-1-methyl-3-nitropyridine by Severin and coworkers[27]. This species displays λ_{max} = 435 nm in methanolic solution, and is quite different from the spectrum of its 1,2-dihydro isomer which has λ_{max} = 520 nm (extinction coefficient = 9500 $M^{-1}cm^{-1}$) in methanolic solution. We have been unable to locate an absorption spectrum of an authentic 1,6-dihydro-3-nitropyridine for comparative purposes. However in view of the close similarity between the reactions of C-3 substituted pyridinium and quinolinium cations discussed above and below, we feel confident in assigning this reduction product as the 1,4-dihydro isomer. It should also be noted that the 1,4-dihydronicotinamide reduction products of 3-cyanopyridinium cations have been definitively identified as the 3-cyano-1,4-dihydropyridines[17].

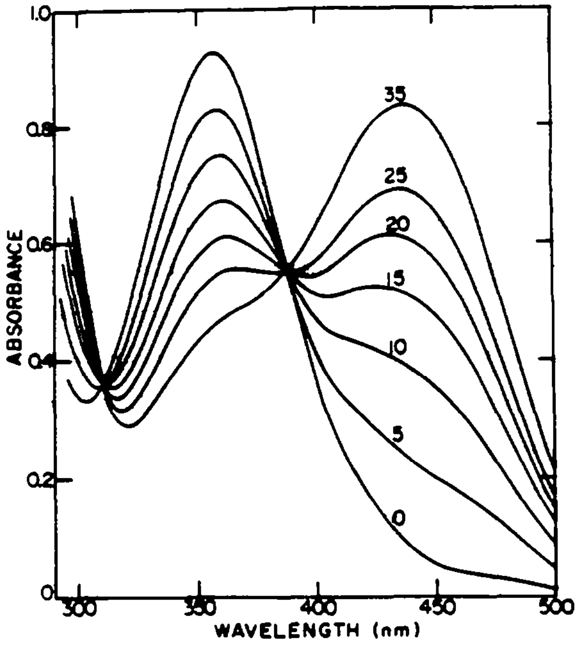


FIGURE 1
Time dependence of the absorption spectrum of an equimolar (1.0 mM) mixture of 1-methyl-3-nitropyridinium bromide and 1-benzyl-1,4-dihydronicotinamide in 20% acetonitrile - 80% water, pH 7, ionic strength 1.0 (KCl) and 25°C (cell path length = 1.0 mm). Spectra are recorded at times (minutes) after initiation of the reaction as indicated on each spectrum.

The rate of increase in absorbance in the vicinity of 440 nm is cleanly kinetically first-order in 1,4-dihydronicotinamide for reactions in which this species is present with 20 - 100 fold excesses of the 1-methyl-3-nitropyridinium cation. Pseudo-first-order rate constants are proportional to the concentration of this pyridinium cation and allow the evaluation of the second-order rate constant $k_2 = 0.72 \pm 0.06\ M^{-1}s^{-1}$ for this reduction in 20% CH_3CN - 80% H_2O at pH 7.0, ionic strength 1.0 and 25°C. Under these same conditions, $k_2 = 0.35 \pm 0.04\ M^{-1}s^{-1}$ for this reaction using 4,4-dideuterio-1,4-dihydronicotinamide as the reductant, and thus $k_2^H/k_2^D = 2.0 \pm 0.3$.

DISCUSSION

Hydroxide Ion Addition

Extensive linear free energy relationships are now available for substituent effects upon both rate and equilibrium data for hydroxide ion addition to quinolinium[19,29] and isoquinolinium[29] cations, and also for the second-order rate constants for reduction of these cations by 1-benzyl-1,4-dihydronicotinamide[14,16]. In addition, there are rate and equilibrium data available for the analogous reactions of acridinium and phenanthridinium cations, while data for a pyridinium cation are presented above. This seems an appropriate time to consider the relative reactivities of these various classes of nitrogen heteroaromatic cations towards both hydroxide ion addition and reduction by 1,4-dihydronicotinamides.

Comparisons of the intrinsic reactivities of these heterocyclic cations towards these reagents, requires comparisons of rate constants for reactions having the same equilibrium constants[24]. For the hydroxide ion addition reactions (pseudobase formation), pK_{R+} values are available for members of all series, and relative intrinsic reactivities towards hydroxide ion simply require comparisons of rate constants for a member of each series at some chosen constant pK_{R+} value. We have chosen to make comparisons at $pK_{R+} = 10.0$, since this is the value observed for pseudobase formation by the 10-methylacridinium cation in aqueous solution at 25°C[30]. This cation is a convenient reference point since it has played a central role in many recent kinetic and mechanistic studies of hydride transfer from 1,4-dihydronicotinamides[1-13], and furthermore is the only acridinium cation, uncomplicated by substituent effects at C-9, for which extensive quantitative data are available for both reduction and pseudobase formation.

Second-order rate constants (k_{OH}) for hydroxide ion attack at C-4 of quinolinium cations and C-1 of isoquinolinium cations, each displaying $pK_{R+} = 10.0$, may be estimated from the relationships in equations [1] and [2], respectively[19,29]. These values are given in Table 1.

$$\log k_{OH} = -0.46\ pK_{R+} + 8.3 \qquad [1]$$

$$\log k_{OH} = -0.36\ pK_{R+} + 8.84 \qquad [2]$$

Hydroxide ion attack occurs at C-6 of phenanthridinium cations[31], although there do not appear to be any reports of rates of hydroxide ion attack upon these cations. However this C-6 site can be considered either as equivalent to C-1 in a series of isoquinolinium cations or alternatively as C-2 in a series of quinolinium cations. In the former case, application of equation [2] gives $k_{OH} = 1.7 \times 10^5\ M^{-1}s^{-1}$ for a phenanthridinium cation of $pK_{R+} = 10.0$. Alternatively, using equation [3][29] for hydroxide ion attack at C-2 of quinolinium cations gives $k_{OH} = 3.4 \times 10^5\ M^{-1}s^{-1}$. The reasonable agreement between these two values suggests that this application of equations [2] and [3] to phenanthridinium cations is acceptable. We have chosen to use the mean of these two values in Table 1.

$$\log k_{OH} = -0.45\ pK_{R+} + 10.03 \qquad [3]$$

TABLE 1

Reactivities of Heteroaromatic Cations of $pK_{R+} = 10.0$ towards Hydroxide Ion and 1-Benzyl-1,4-dihydronicotinamide

Cation	k_{OH}[a]	k_2[b]	k_2/k_{OH}	Rel. k_2/k_{OH}
Acridinium	550[c]	400[d]	0.73	1.6×10^5
Quinolinium (C-4)	5000	80	0.016	3400
Pyridinium (C-4)	800	0.3	3.8×10^{-4}	80
Quinolinium (C-2)	3.4×10^5	<8[e]	$<2\times10^{-5}$	<4
Phenanthridinium	2.5×10^5	0.8	3.2×10^{-6}	0.7
Isoquinolinium	1.7×10^5	0.8	4.7×10^{-6}	1.0

[a] Second-order rate constant ($M^{-1}s^{-1}$) for hydroxide ion attack; calculated as described in text unless indicated otherwise.

[b] Second-order rate constant ($M^{-1}s^{-1}$) for reduction by 1-benzyl-1,4-dihydronicotinamide in 20% CH_3CN - 80% H_2O, ionic strength 1.0, 25°; calculated as described in text unless indicated otherwise.

[c] From reference (30).

[d] From reference (13).

[e] Not readily accessible, but much smaller than for attack at C-4 since no 1,2-dihydroquinoline is observable in the pmr spectra of the reaction products[14]; we have conservatively estimated the rate of attack at C-2 as less than 10% of the rate of attack at C-4.

The 1-methyl-3-nitropyridinium cation that has been studied in the current work has $pK_{R+} = 9.42$ for pseudobase formation at C-4, which is quite close to

pK_{R+} = 10.0 which we have chosen as a reference point. On the assumption that the slope of the log k_{OH} v. pK_{R+} relationship is similar for pyridinium and quinolinium cations (i.e. -0.46 as in equation [1]), we can use k_{OH} = 1600 $M^{-1}s^{-1}$ reported above for the 1-methyl-3-nitropyridinium cation to generate equation [4] for hydroxide ion attack at C-4 of pyridinium cations. This equation then predicts k_{OH} = 800 $M^{-1}s^{-1}$ for a pyridinium cation of pK_{R+} = 10.0.

$$\log k_{OH} = -0.46\ pK_{R+} + 7.5 \qquad [4]$$

Reduction by 1-Benzyl-1,4-dihydronicotinamide

Comparison of intrinsic reactivities towards reduction by 1,4-dihydronicotinamides, requires comparison of reactions having the same equilibrium constants for hydride transfer. We are able to make comparisons using 1-benzyl-1,4-dihydronicotinamide as a constant hydride donor species. In principle, it should be possible to obtain reasonable estimates for the equilibrium constants for hydride transfer between the heterocyclic cations A^+ and B^+ in equation [5] from the equilibrium constants for hydroxide ion transfer in the virtual reaction in equation [6].

$$A^+ + BH \xrightleftharpoons{K_H} AH + B^+ \qquad [5]$$

$$A^+ + BOH \xrightleftharpoons{K_{OH}} AOH + B^+ \qquad [6]$$

Thus, $K_H = [AH][B^+]/[A^+][BH]$ and $K_{OH} = [AOH][B^+]/[A^+][BOH]$, and $\log K_{OH} = pK^B_{R+} - pK^A_{R+}$ should be a close approximation to $\log K_H$. Now for a constant hydride donor BH (i.e. 1-benzyl-1,4-dihydronicotinamide) reacting with a series of heteroaromatic cations A^+ (pyridinium, quinolinium, isoquinolinium, phenanthridinium and acridinium), reactions having equal K_H may simply be chosen from cations of equal pK_{R+}. Therefore the reduction by 1-benzyl-1,4-dihydronicotinamide of a series of cations all having pK_{R+} = 10.0 should approximate a series of reactions all having similar K_H equilibrium constants.

The second-order rate constants (k_2) for reduction of quinolinium (at C-4) and isoquinolinium cations by 1-benzyl-1,4-dihydronicotinamide are related to the pK_{R+} values of these cations by equations [7] and [8], respectively[14,16]. These equations predict the k_2 values listed in Table 1 for quinolinium and isoquinolinium cations of pK_{R+} = 10.0.

$$\log k_2 = -0.56\ pK_{R+} + 7.3 \qquad [7]$$

$$\log k_2 = -0.50\ pK_{R+} + 4.9 \qquad [8]$$

Roberts et al.[10] have reported rate constants for reduction of the 5-methylphenanthridinium cation by 1,4-dihydronicotinamide derivatives in 4:1 2-propanol - water mixed solvent at 25°C. These data indicate the relative rates of reduction of the 10-methylacridinium and 5-methylphenanthridinium cations by the same 1,4-dihydronicotinamide derivative to be 5000:1 in favor of the acridine derivative. Using this ratio, and $k_2 = 400\ M^{-1}s^{-1}$ for the 10-methylacridinium cation in our 20% CH_3CN - 80% H_2O solvent system[13], we estimate $k_2 = 0.08\ M^{-1}s^{-1}$ for the reduction of the 5-methylphenanthridinium cation by 1-benzyl-1,4-dihydronicotinamide in our solvent system. This estimate is in excellent agreement with $k_2 = 0.085\ M^{-1}s^{-1}$ estimated from equation [8] when the 5-methylphenanthridinium cation ($pK_{R+} = 11.94$[31]) is treated as an isoquinolinium cation. Thus we can confidently use equation [8] to predict $k_2 = 0.8\ M^{-1}s^{-1}$ for a phenanthridinium cation of $pK_{R+} = 10.0$.

If it is assumed that the slope of the log k_2 v. pK_{R+} correlation in equation [7] for the reduction at C-4 of quinolinium cations is also applicable to the C-4 reduction of pyridinium cations, then equation [9] can be calculated for the reduction of pyridinium cations using the data reported above for the 1-methyl-3-nitropyridinium cation. This equation allows the estimation of $k_2 = 0.3\ M^{-1}s^{-1}$ for the C-4 reduction of a pyridinium cation of $pK_{R+} = 10.0$.

$$\log k_2 = -0.56\ pK_{R+} + 5.1 \qquad [9]$$

As a further test of equation [9], we may use it to predict $k_2 = 8 \times 10^{-4}\ M^{-1}s^{-1}$ for the degenerate hydride transfer between 1-benzyl-1,4-dihydronicotinamide and the 1-benzylnicotinamide cation ($pK_{R+} = 14.6$[14]). This value is in reasonable agreement with a value of $7 \times 10^{-4}\ M^{-1}s^{-1}$ which we have estimated for this reaction in our solvent system. This estimate was based upon the rate constant $k_2 = 0.119\ M^{-1}min^{-1}$ reported by van Eikeren and Grier[32] for this degenerate hydride transfer in 25% CH_3CN - 75% H_2O at 40°C, and our experimentally measured relative rates of reduction (2.7:1) for reaction of the 1-methylnicotinonitrile cation with 1-benzyl-1,4-dihydronicotinamide under these conditions and in our own standard solvent system at 25°C.

Relative Reactivities

From the second-order rate constants summarized in Table 1 for a series of cations of constant pK_{R+} value, the intrinsic reactivities of these classes of cations towards both hydroxide ion attack and 1,4-dihydronicotinamide reduction can be calculated. It is immediately obvious that the rates of hydroxide ion attack at C-4 of pyridinium and quinolinium and at C-9 of acridinium cations are much slower than at C-1 of isoquinolinium cations, C-2 of quinolinium cations or C-6 of phenanthridinium cations. These data suggest that rates of formation of 1,2-dihydropyridine derived ring systems upon hydroxide ion addition are intrinsically faster than the rates of formation of 1,4-dihydropyridine derivatives, and this phenomenon is further demonstrated in the current work by the kinetic control of pseudobase formation at C-2 of the 1-methyl-3-nitropyridinium cation, even though the thermodynamically more stable pseudobase is the C-4 hydroxide adduct.

On the other hand the rates of reduction by 1-benzyl-1,4-dihydronicotinamide are much greater for quinolinium (at C-4) and acridinium cations than for the phenanthridinium and isoquinolinium cations. It has also recently been shown[14,33] that 1-benzyl-1,4-dihydronicotinamide reduction of quinolinium cations occurs much more rapidly at C-4 than at C-2, and this is also true for reduction of two classes of C-3 substituted pyridinium cations (3-CN[17] and 3-NO_2 (present work)). Comparison of relative reactivities (k_2/k_{OH}) of each cation towards reduction and hydroxide ion attack, indicates that the acridinium, quinolinium (at C-4) and pyridinium cations all display dramatically enhanced reactivities for 1,4-dihydronicotinamide reduction relative to the isoquinolinium and phenanthridinium cations. Interestingly, k_2/k_{OH} for C-2 of quinolinium cations for formation of 1,2-dihydropyridine type systems seems to be of the same magnitude as this ratio for the isoquinolinium and phenanthridinium systems.

It seems reasonable to assume that the relative reactivities of these cations towards hydroxide ion will be reasonably representative of the intrinsic reactivities of these classes of heteroaromatic cations towards nucleophilic attack in general. The strongest argument against such an assumption, namely the possibility of different solvation effects for hydroxide ion attack upon these various classes of cations, is allayed by the observation of similar entropies of activation for hydroxide ion attack upon an acridinium cation and an isoquinolinium cation[30]. We have recently[15,16] shown that the reduction of isoquinolinium cations by 1,4-dihydronicotinamides proceeds via a transition state species in which the migrating hydrogen is quite "hydridic", and thus nucleophilic, in character. If similar attacks by "hydridic" species were rate-determining for the reduction of acridinium, quinolinium (at C-4) and pyridinium (at C-4) cations one might expect that the relative reactivities of the cations in Table 1 should be at least qualitatively similar for both 1,4-dihydronicotinamide reduction and hydroxide ion attack. The dramatically enhanced rates of dihydronicotinamide reduction that are observed in Table 1 for acridinium, quinolinium (C-4) and pyridinium cations are thus apparently inconsistent with a simple nucleophilic attack in the rate-determining transition state for all cations in this Table. Rather, these data imply that a mechanism more facile than simple hydride transfer is available for the formation of 1,4-dihydropyridine derivatives but not for 1,2-dihydropyridine derivatives.

Consistent with these ideas, we have recently argued for an $e^- + H\cdot$ mechanism for reduction of acridinium cations in predominantly aqueous media[13], and either $e^- + H\cdot$ or $e^- + H^+ + e^-$ for reduction of quinolinium[14] and pyridinium[17] cations. Such mechanisms, involving one electron transfer steps, must of course proceed via radical intermediates. The relative reactivities of acridinium > quinolinium > pyridinium observed in Table 1 are consistent with the expected relative stabilities of radical intermediates in such systems. Thus the increasing benzylic radical stabilization available to the members of this series appears as increasing intrinsic reactivities for cations which are matched thermodynamically.

It should also be noted that $k_2^H/k_2^D = 2.0$ reported above for the reduction of the 1-methyl-3-nitropyridinium cation is similar to the values previously found for reduction of the 10-methylacridinium (1.56[13]) and the more reactive of the C-3 substituted 1-methylquinolinium cations (1.8 for 3-CN; 1.5 for 3-NO_2[14]) in predominantly aqueous reaction media. These kinetic isotope effects are much smaller than the range of $k_2^H/k_2^D = 4.4 - 6.6$ reported[11,15,20,22] for reductions which are believed to be genuine one-step hydride transfer processes. These low isotope effects for C-4 reduction are consistent with electron transfer being partly rate-determining in these cases.

The approach that we have taken in the estimation of equilibrium constants K^H from pK_{R+} values for pseudobase formation is similar to that used by Breslow and coworkers[34,35] in the thermodynamic cycles that form the basis of their studies of the acidities of very weak carbon acids. There have recently also been some attempts made to directly measure K_H values for some of the hydride transfer equilibrations that are represented by equation (5)[10,21,22,36]. For a reaction which lies heavily in favor of one side of equation (5), the rate constant for the thermodynamically favored process is readily available directly. With this rate constant available, the rate constant for the back reaction and thus the equilibrium constant are then evaluated via an iterative procedure for fitting the time-dependence of spectrophotometric data for the small amount of this back reaction that occurs when equilibrium is approached from the side of the final thermodynamically favored reactant pair[21].

We feel that equilibrium constants evaluated by this procedure are subject to relatively large experimental uncertainties, although it must be admitted that impressive agreement is reported in several cases in which the same large equilibrium constant is estimated by two somewhat different ladder procedures[36]. In particular, Roberts et al.[10] quote $K_H = 4.4 \times 10^{11}$ for the reaction of the 10-methylacridinium cation with 1-methyl-1,4-dihydro-N-benzylnicotinamide and $K_H = 1.1 \times 10^5$ for the reaction of the 5-methylphenanthridinium cation with this same reducing agent. This factor of 4×10^6 by which these equilibrium constants differ is far larger than expected on the basis of the pK_{R+} values for these two tricyclic cations; i.e. $10^{(11.94-10.0)} = 100$.

In making such comparisons it should be kept in mind that we have only used

pK_{R+} values for strictly aqueous solutions whereas all the direct measurements of K_H from Kreevoy's laboratory refer to 80% 2-propanol - 20% water as solvent. There is clearly a possibility for differential solvation effects for various cations for both the hydride transfer and pseudobase formation reactions in such comparisons.

The presence of a quite strong solvent effect upon pK_{R+} can be seen from pK_{R+} = 5.3 reported for the 1-benzyl-3-cyanoquinolinium cation in 80% 2-propanol - 20% water[21] and pK_{R+} = 9.0 for the corresponding 1-methyl-3-cyanoquinolinium cation in strictly aqueous solution[19]. However, for the reduction of quinolinium cations by 9,10-dihydro-10-methylacridine, Kreevoy and Lee[21] report that there is a close linear correlation of log K_H with log K_{R+}, and furthermore the slope of this correlation line is 1.0 within experimental error. However this correlation seems to break down for a more structurally diverse set of dihydro heterocycles reacting with the 10-methylacridinium cation[36]. Unfortunately, these pK_{R+} values in aqueous 2-propanol are themselves complex constants which contain contributions from both the hydroxide and the alkoxide adducts in the mixture of pseudobase species. It is thus not clear whether significant variations in the alkoxide/hydroxide pseudobase ratio between different heterocycles may not be influencing the expected log K_H v. pK_{R+} correlation. In this sense, our own current comparisons between pseudobase formation in aqueous solution and 1,4-dihydronicotinamide reduction in 20% acetonitrile - 80% water would be expected to be much less influenced by any differential solvation effects.

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