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REVIEW

Merged Mechanisms for Hydride Transfer from 1,4-Dihydronicotinamides

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Recent work on the reduction of heteroaromatic cations by 1,4-dihydronicotinamides and related reducing agents is reviewed. Extensive correlations are presented between the second-order rate constants (k_2) for these reactions and the second-order rate constants (k_{OH}) and equilibrium constants (pK_{R^+}) for hydroxide ion attack on these cations. Close correlations of log k_2 with the electron affinities and one-electron reduction potentials of these cations are also presented. These relationships are considered in the context of a direct hydride transfer from donor to acceptor and also in terms of SET mechanisms which are also commonly discussed for such reactions. It is shown that the interpretation of these formal hydride transfer reactions in terms of an imbalanced development of electronic charge and C–H bond fission within the transition state species leads to a rational merging of the single-step hydride transfer mechanism and the SET mechanisms. The structures of the transition state species are expected to be highly variable and quite dependent upon the nature of the hydride donor and acceptor species, with considerable contribution from charge-transfer interactions. Such imbalanced transition state species are analyzed in terms of two different types of reaction coordinate diagrams and also in terms of the valence bond configuration mixing theory.

INTRODUCTION

The elucidation of the mechanistic details of formal hydride ion transfers between organic molecules and ions, in reactions which are related to the chemistry of the nicotinamide coenzymes, continues to be an active area of investigation in bioorganic chemistry (*1–5*). The first truly mechanistic consideration of such processes seems to have been the report of Mauzerall and Westheimer in 1955 (*6*) on the reduction of a variety of organic species by simple N-substituted 1,4-dihydronicotinamides. They demonstrated the direct transfer of deuterium from C-4 of 1-benzyl-4-deuterio-1,4-dihydronicotinamide to the malachite green cation (bis(4-dimethylaminophenyl)-phenylmethyl cation), and also observed the reduction of the 1,1-diphenyl-2-picrylhydrazyl radical by 1,4-dihydronicotinamides. In view of this latter observation, they suggested the possibility of a radical mechanism for these reductions, and so this initial mechanistic study of "A Model for Reduced DPN" introduced the concept of hydride transfer via a mechanism involving a single electron transfer (SET) step. In a subsequent report (*7*) from the same

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laboratory 2 years later on the reduction of thiobenzophenones by 1-benzyl-1,4-dihydronicotinamide, Westheimer and co-workers deduced a "direct transfer of a hydride ion from the dihydro compound to the thioketone" on the basis of substituent effects, kinetic isotope effects, solvent effects, and the lack of any influence of pH or dissolved oxygen upon the rates of these reactions. Thus even after only the first two mechanistic studies in this area, the possibility of alternative mechanisms for these formal hydride transfer reactions had been suggested.

The differentiation between SET mechanisms and direct one-step hydride transfer processes has been the target of numerous subsequent studies of the mechanisms of nonenzymic hydride transfers in model systems for nicotinamide coenzyme redox reactions. Such studies have led to considerable controversy, with some workers claiming on various kinetic and thermodynamic grounds that SET mechanisms are not possible, while others present experimental "proof" for SET mechanisms (*1–5*, *8–29*). An essentially independent controversy on the same subject has also been proceeding in the Russian literature (*5*, *30–32*). The discordant views in this area can be considered as a subset of a broad range of discussions regarding SET that have emerged recently for a variety of reactions of nucleophilic species (*33–43*).

Many of the nonenzymic studies of hydride transfer have employed a reaction of the type described by Eq. [1], in which a dihydropyridine derivative is used to reduce a nitrogen heteroaromatic cation. This reaction formally involves hydride transfer from a donor (HD) to an acceptor (A^+), and can be considered a hydride transfer between two heteroaromatic cations.

$$\mathrm{HD} + \mathrm{A}^+ \xrightarrow{k_2} \mathrm{D}^+ + \mathrm{HA} \qquad [1]$$

Investigations in our laboratory have shown that the reductions of both isoquinolinium (*44*, *45*) and 3,4-dihydroisoquinolinium (*46*) cations by 1,4-dihydronicotinamides require the migrating hydrogen to bear excess negative charge in the transition state and to be quite hydridic in character. However, the extension of these investigations to a variety of other cationic acceptors has generated a number of experimental observations which indicate that either a highly variable transition state structure or a change in reaction mechanism must be seriously considered (*47–50*).

There is now a significant amount of literature (*51*, *52*) relating to the reduction of a variety of pyridinium, quinolinium, isoquinolinium, acridinium, phenanthridinium, xanthylium, and tropylium cations as the formal hydride acceptors (A^+), by various 1,4-dihydropyridines, 9,10-dihydroacridines, 1,4-dihydroquinolines, and 5,6-dihydrophenanthridines as the formal hydride donors (HD). In this current paper, the data that have been collected in this author's laboratory are considered in conjunction with the reactivities of these cationic acceptors toward nucleophilic attack, and these data are also compared with various single electron transfer properties of these cations. These studies allow the proposal of a unified mechanism for these hydride transfer processes, and lead to a rationalization of a large number of earlier experimental observations.

POSSIBLE MECHANISMS

The three most commonly considered mechanisms for the reductions of Eq. [1] are outlined in Schemes 1–3. Scheme 1 represents the direct one-step migration of a hydride ion from HD to A^+ via a transition state species in which a fractional negative charge develops upon the migrating hydrogen atom (electrical neutrality requires $d + a - h = 1$). Scheme 2 shows a two-step process; initial electron transfer, followed by migration of a neutral hydrogen atom (e^-, $H^{\cdot}$). Scheme 3 represents the stepwise transfer of an electron, followed by a proton, and then a second electron (e^-, H^+, e^-).

$$\mathrm{HD} + \mathrm{A}^+ \longrightarrow [\overset{+d}{\mathrm{D}} \cdots \overset{-h}{\mathrm{H}} \cdots \overset{+a}{\mathrm{A}}] \longrightarrow \mathrm{D}^+ + \mathrm{HA}$$

Scheme 1

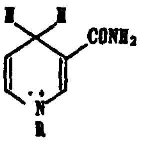
$$\mathrm{HD} + \mathrm{A}^+ \longrightarrow [\mathrm{HD}^{\cdot+}\ \mathrm{A}^{\cdot}]$$
$$[\mathrm{HD}^{\cdot+}\ \mathrm{A}^{\cdot}] \longrightarrow \mathrm{D}^+ + \mathrm{HA}$$

Scheme 2

$$\mathrm{HD} + \mathrm{A}^+ \longrightarrow [\mathrm{HD}^{\cdot+}\ \mathrm{A}^{\cdot}]$$
$$[\mathrm{HD}^{\cdot+}\ \mathrm{A}^{\cdot}] \longrightarrow [\mathrm{D}^{\cdot}\ \mathrm{HA}^{\cdot+}]$$
$$[\mathrm{D}^{\cdot}\ \mathrm{HA}^{\cdot+}] \longrightarrow \mathrm{D}^+ + \mathrm{HA}$$

Scheme 3

In each of Schemes 2 and 3, caged radical pairs are indicated as intermediate species. This representation is adopted since in general this class of reduction reactions does not display chemistry that is typical of the individual radical species. A formal electron transfer from the donor (HD) to a cationic acceptor (A^+) would produce a radical cation ($HD^{\cdot+}$) and a neutral radical ($A^{\cdot}$). Dihydronicotinamide radical cations ($HD^{\cdot+}$) such as **1**, which would be formed when a 1,4-dihydronicotinamide is the reductant, are known to be very unstable in aqueous solution (*53–57*). Such species decompose by rapid proton loss from C-4 to give the neutral pyridinyl radical ($D^{\cdot}$) (**2**). Such loss of hydrogen to solvent from C-4 of HD is not typical of the vast majority of examples of Eq. [1], which normally involve direct transfer of hydrogen from HD to A^+ without exchange with solvent protons.



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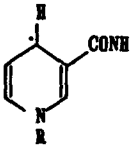

2

The radical **2** is an example of the $D^{\cdot}$ species in Scheme 3. As well as being generated by deprotonation of $HD^{\cdot +}$, such species have also been much studied as the one-electron reduction products of nicotinamide cations and are spectroscopically observable in such processes (*9, 56, 58–60*). Although in general, $D^{\cdot}$ show greater stability than the analogous $HD^{\cdot +}$, these $D^{\cdot}$ species usually undergo rapid dimerization (*58–60*). Such dimerization products are not usually observed for the nicotinamide coenzyme model systems of Eq. [1].

When A^+ represents an heteroaromatic cation (pyridinium, quinolinium, isoquinolinium, acridinium, phenanthridinium), the $A^{\cdot}$ and $HA^{\cdot +}$ species of Schemes 2 and 3 also represent pyridine-derived neutral radicals and radical cations, respectively. The stabilities and reactivities of these species would be expected to be similar to those described above for the corresponding nicotinamide radicals, and their existence within radical cages would be required to prevent side reactions. All reactions within such cages must be faster than dissociation of the radical pairs to account for the absence of any significant amount of byproducts from these individual radical species.

Interactions between the components of the cage-paired species are presumably mainly of hydrophobic and/or charge-transfer type. Charge-transfer interactions of heteroaromatic cations with suitable electron donor species are well known (*61*). In fact, it is likely that charge-transfer complexation between the 1,4-dihydronicotinamide donor and the heteroaromatic cation acceptor should be included as an initial step in each of Schemes 1, 2, and 3. All subsequent steps in these schemes should then be viewed as occurring within these 1 : 1 complexes. A charge-transfer complex has indeed been observed during the reaction of 1-benzyl-1,4-dihydronicotinamide with acridinium cations (*47, 62*), while a model for the formation of species of the type $[HD^{\cdot +}\ A^{\cdot}]$ is available from the interaction of tetramethylphenylenediamine with acridinium cations (*47*).

REDUCTION vs NUCLEOPHILIC ADDITION

Consider the reduction of a series of heteroaromatic cations via a reaction mechanism in which the migrating hydrogen species has significant hydridic character in the rate-determining transition state. To a first approximation, one might expect that the relative reactivities of these cationic acceptors toward reduction would be similar to their relative reactivities toward attack by other nucleophiles. Indeed, for a series of substituted isoquinolinium cations, a linear free energy relationship has been found between the rates of reduction by 1-benzyl-1,4-dihydronicotinamide and the rates of hydroxide ion attack at the same electrophilic center (*45*). Such reductions of isoquinolinium cations by 1,4-dihydronicotinamides have been unambiguously established (*44*) as involving a transition state species which has significant hydridic character upon the migrating hydrogen atom.

The hydroxide ion is the nucleophile of choice for comparisons with the formal hydride transfers of 1,4-dihydronicotinamide reductions, since extensive quantitative rate and equilibrium data are now available for the attack of this nucleophile upon a wide range of heteroaromatic cations (*96*). The addition of hydroxide ion to

TABLE I

Rate Constants for the 1-Benzyl-1,4-dihydronicotinamide Reduction and Hydroxide Ion Addition to Heteroaromatic Cations[a]

No.	Cation	pK_{R^+}	k_2 (M^{-1} s^{-1})	k_{OH}(M^{-1} s^{-1})	k_2/k_{OH}	EA (eV)	$-E_{1/2}$ (V)
	⟨P4 Cations[b]⟩						
1	Pyridinium	20.5(63)	4.2×10^{-7}(52)	1.1×10^{-2}(52)	3.8×10^{-5}	5.0	1.269
2	3-CONH$_2$[c]	14.6(48)	7.5×10^{-4}(50)	6[d]	1.3×10^{-4}	5.5	0.97[h]
3	3-CN	12.2(63)	1.84×10^{-2}(49)	77[d]	2.4×10^{-4}	5.6	0.76
4	3-CN[c]	11.2[e]	9.2×10^{-2}(49)	220[d]	4×10^{-4}	5.7	
5	3-NO$_2$	9.42(50)	0.72(50)	1.6×10^{3}(50)	4.5×10^{-4}		
6	Quinolinium	17.4(64)	5.0×10^{-3}(48)	2(64)	2.5×10^{-3}	5.6	0.842
7	3-Br	15.1(64)	0.33(48)	23(64)	1.4×10^{-2}		0.65[h]
8	3-CONH$_2$	12.18(64)	2.8(48)	450(64)	6.2×10^{-3}		
9	3-CO$_2$CH$_3$	11.28(64)	14.3(48)	1040(64)	1.4×10^{-2}		
10	3-CN	9.06(64)	121(48)	1.6×10^{4}(64)	7.6×10^{-3}		0.49[h]
11	3-NO$_2$	6.82(65)	6.5×10^{3}(48)	1.3×10^{5}(65)	5.0×10^{-2}		
12	Acridinium	10.01(66)	400(47)	550(66)	0.73	6.1	0.319
13	Tropylium	4.76(67)	2.5×10^{4}(52)	3.1×10^{5}(67)	8.1×10^{-2}	6.24	0.265[i]
14	Xanthylium	−0.83(68)	2.7×10^{8}(52)	3.5×10^{7}(69)	7.7	6.75	−0.21[j]
	⟨P2 Cations[b]⟩						
7′	3-Br-quinolinium	12.34(64)	0.05[f]	2.8×10^{4}[g]	1.8×10^{-6}		0.65[h]
15	Isoquinolinium	16.3(71)	8.0×10^{-4}(45)	940(72)	8.5×10^{-7}	5.4	1.046
16	4-Br	13.8(72)	1.8×10^{-2}(45)	7.0×10^{3}(72)	2.6×10^{-6}		
17	4-CONH$_2$	11.49(72)	4.6×10^{-2}(45)	2.8×10^{4}(72)	1.6×10^{-6}		
18	4-COC$_6$H$_5$	9.34(72)	0.79(45)	4.1×10^{4}(72)	1.9×10^{-5}		
19	4-CN	7.80(72)	29(45)	8.0×10^{5}(72)	3.6×10^{-5}		
20	5-NO$_2$	11.7(73)	0.12(44)	4.2×10^{4}[g]	2.9×10^{-6}		
21	Phthalazinium	11.04(74)	4.0×10^{-2}(45)	6.2×10^{4}(72)	6.5×10^{-7}		0.861
22	5-NO$_2$	7.87(72)	3.29(45)	4.7×10^{6}(72)	6.9×10^{-7}		
23	Phenanthridinium	11.94(75)	0.08(50)	4.0×10^{4}(50)	2.0×10^{-6}		
24	3,4-Dihydroisoquinolinium[c]	10.93(46)	1.9×10^{-2}(46)	3.4×10^{5}(46)	5.6×10^{-8}		

[a] All nitrogen heteroaromatic cations are the *N*-methyl cations unless indicated otherwise. pK_{R^+} values and rate constants are taken from the references indicated by the integers in parentheses. k_2 values are in 20% acetonitrile–80% water at ionic strength 1.0 and 25°C. k_{OH} values are for aqueous solution, ionic strength 0.1 at 25°C. Electron affinities (EA) are from the compilations in Refs. *(76)* and *(77)*. $-E_{1/2}$ (vs S.C.E.) are from Ref. *(121)* unless otherwise indicated.

[b] Class P4 cations give 1,4-dihydropyridine derivatives as reduction products; P2 cations give 1,2-dihydropyridines. k_{OH} values are for hydroxide ion addition to the carbon atom that is the reduction site.

[c] *N*-benzyl cation.

[d] Calculated from a linear free energy relationship *(50)*.

[e] Estimated using pK_{R^+}(N-CH$_3$) − pK_{R^+}(N-CH$_2$C$_6$H$_5$) ≈ 1.0 *(63)*.

[f] Calculated from the observed 6 : 1 ratio for C-4 vs C-2 attack in the reduction of this cation *(48)*.

[g] Calculated from a linear free energy relationship *(70)*.

[h] Data from Ref. *(122)* have been corrected by 0.11 V to bring these potentials onto the same scale as the data for the *N*-methyl quinolinium and acridinium cations in Ref. *(121)*.

[i] From Ref. *(123)*.

[j] By interpolation of the data in Fig. 1 of Ref. *(82)*.

heterocyclic cations, which is commonly referred to as pseudobase formation, is represented by Eq. [2], where k_{OH} is the second-order rate constant for this reaction. The equilibrium constant for Eq. [2] is usually defined by $K_{R^+} = [H^+][AOH]/[A^+]$, so that p$K_{R^+}$ is exactly analogous to the pK_a value of a Brønsted acid. Table 1 summarizes the second-order rate constants (k_2) for the reduction of 24 cations (A^+) by 1-benzyl-1,4-dihydronicotinamide (HD of Eq. [1]) under constant

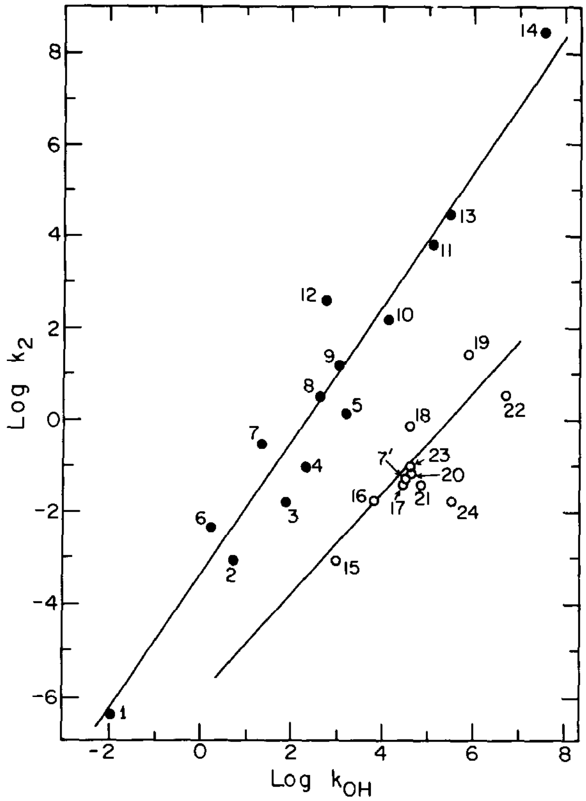

FIG. 1. Dependence of log k_2 upon log k_{OH} for P2 cations (○) and P4 cations (●). Numerals identify the cations in Table 1. Upper and lower lines are calculated from Eqs. [3] and [4], respectively.

experimental conditions (20% acetonitrile–80% water, ionic strength 1.0, 25°C), and also the second-order rate constants (k_{OH}) and equilibrium constants (pK_{R^+}) for hydroxide ion attack upon each of these cations in aqueous solution according to Eq. [2].

$$A^+ + {}^-OH \overset{k_{OH}}{\rightleftharpoons} AOH \qquad [2]$$

An examination of the relationship between k_2 and k_{OH} leads to Fig. 1. From this figure it is clear that there is no simple general relationship between the rate constants for nucleophilic attack by hydroxide ion and the rate constants for the reduction of these cations by 1-benzyl-1,4-dihydronicotinamide. However, a subclassification of these data does appear to lead to the two useful correlation lines that are identified in Fig. 1. Thus, all cations that give 1,4-dihydropyridine reduction products (from pyridinium, quinolinium, or acridinium cations), determine a single correlation line (Eq. [3]); cations that give 1,2-dihydropyridine products (from isoquinolinium, phthalazinium, quinolinium (at C-2), and phenanthridinium cations) require a distinctly different correlation line (Eq. [4]). For convenience, we will refer to these two classes of cations as Class P4 (Eq. [3]) and Class P2 (Eq.

[4]), respectively. The 2-benzyl-3,4-dihydroisoquinolinium cation, which is the only acceptor in Fig. 1 in which reduction does not occur in an aromatic ring, appears to fall below the correlation line for the isoquinolinium cations, and has not been considered in the derivation of Eq. [4].

$$\log k_2 = 1.5(\pm 0.1) \log k_{\mathrm{OH}} - 3.6(\pm 1.0) \qquad (r = 0.966) \qquad [3]$$

$$\log k_2 = 1.1(\pm 0.2) \log k_{\mathrm{OH}} - 6.1(\pm 0.6) \qquad (r = 0.892) \qquad [4]$$

Cations that produce 1,4-dihydropyridine derivatives as reduction products display k_2/k_{OH} ratios which cover a 2×10^5-fold range (3.8×10^{-5} to 7.7), whereas the range of k_2/k_{OH} for P2 cations is only 50-fold (6.5×10^{-7} to 3.6×10^{-5}). Thus in general this ratio is greater for P4 cations than for P2 cations, and is also much more variable for P4 cations than for P2 cations. It should be noted that the C-2 reactions of the 3-bromo-1-methylquinolinium cation (7′), which is the only quinolinium cation for which rate data are available for reduction at C-2, clearly fall with the isoquinolinium cations. As expected, the C-4 reactions of this same quinolinium cation fall on the Class P4 correlation line. It is also clear from Fig. 1 that even though the tropylium and xanthylium cations are not nitrogen heterocycles, they can nevertheless be considered as members of the Class P4 cations.

The quite different regiochemistries that are observed for the kinetic control of the reactions of quinolinium cations with hydroxide ion (predominant C-2 attack (*64*)) and with 1-benzyl-1,4-dihydronicotinamide (predominant C-4 reduction (*48*, *78*)), also point to an important distinction between the P2 and the P4 series of cations. It should also be noted that borohydride ion reduction of quinolinium cations, unlike 1,4-dihydronicotinamide reduction, occurs preferentially at C-2 (*78*). It is thus clear that there must be significant differences between the detailed description of the migrating "hydride" species in the transition state depending upon whether the source of that "hydride" unit is a borohydride ion or a 1,4-dihydronicotinamide molecule. The presence of a fractional negative charge ("hydridic character") on the migrating hydrogen species has been established (*44*, *45*) for the reduction of isoquinolinium cations (P2 cations) by 1,4-dihydronicotinamides. The profound kinetic preference for C-4 attack in the reduction of quinolinium cations by 1,4-dihydronicotinamides then suggests that the migrating hydrogen atom in these reductions (of P4 cations) might not have significant hydridic character in the rate-determining transition state species.

Closer examination of the data in Fig. 1 suggests that isoquinolinium, pyridinium (C-4), and quinolinium (C-4) cations are distinct families as represented by the lines in Fig. 2. The lines for the pyridinium and quinolinium cations appear to be parallel (slope 1.2). Furthermore, the data for the π-isoelectronic 10-methylacridinium and xanthylium cations appear to describe a further line of slope 1.2. For a constant susceptibility to nucleophilic attack, as defined by k_{OH}, the relative susceptibilities to dihydronicotinamide reduction (k_2) are: acridinium > quinolinium > pyridinium > isoquinolinium. This relationship is expressed numerically in Table 2, for $k_{\mathrm{OH}} = 550\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$, which is chosen because it represents k_{OH} for the *N*-methyl acridinium cation. These data are discussed in more detail below.

The classification of heterocyclic cations into the structurally related groups that are indicated in the rate–rate correlations of Fig. 2 is also apparent in the

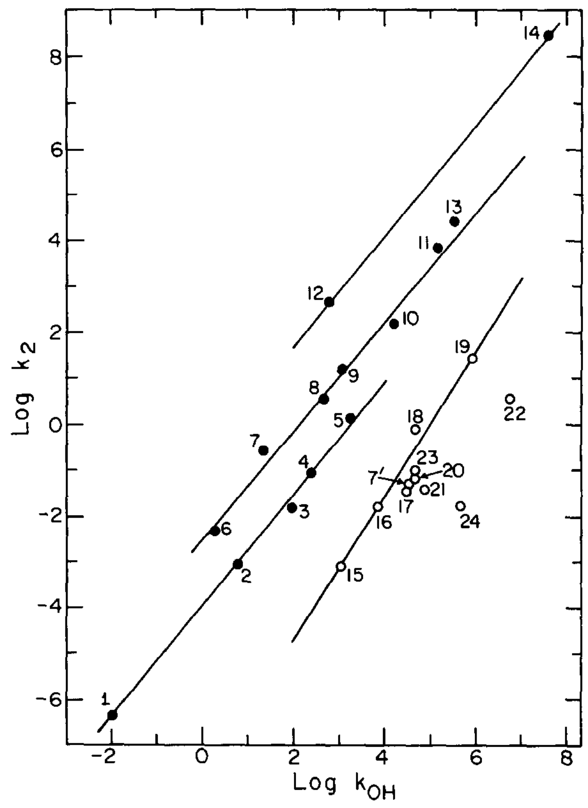

FIG. 2. Dependence of log k_2 upon log k_{OH} for various structural classes of cationic acceptors (Table 1). Lines (from top to bottom) represent data for acridinium and xanthylium cations (12 and 14; slope = 1.21), quinolinium cations (6–11; slope = 1.18), pyridinium cations (1–5; slope = 1.22) and isoquinolinium cations (15–20; slope = 1.55).

TABLE 2

Relative Reactivities of Heteroaromatic Cations Toward Reduction

	Acridinium	Quinolinium	Pyridinium	Isoquinolinium
At $pK_{R+} = 10.0$[a]				
$k_2(\text{M}^{-1}\ \text{s}^{-1})$	400	70	0.35	0.8
Rel. k_2	1100	200	(1)	2.3
$k_{OH}(\text{M}^{-1}\ \text{s}^{-1})$	550	5000	800	8.5×10^5
Rel. k_{OH}	0.7	6	(1)	100
k_2/k_{OH}	0.73	0.015	4×10^{-4}	9×10^{-6}
Rel. k_2/k_{OH}	1900	40	(1)	0.012
At $k_{OH} = 550\ \text{M}^{-1}\ \text{s}^{-1}$				
$k_2\ (\text{M}^{-1}\ \text{s}^{-1})$	400	6[b]	0.2[b]	3×10^{-4} [b]
Rel. k_2	2000	30	(1)	0.0015

[a] By interpolation at $pK_{R+} = 10.0$ in Figs. 3–5.
[b] By interpolation on the lines in Fig. 2.

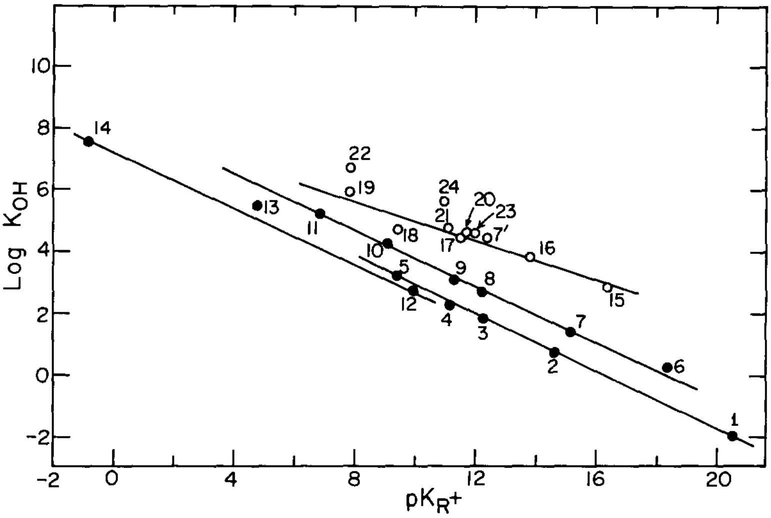

FIG. 3. Dependence of log k_{OH} upon pK_{R^+} for cations from Table 1. Lines (top to bottom) represent data for isoquinolinium cations (15–20; slope = −0.30), quinolinium cations (6–11; slope = −0.46), pyridinium cations (1–5; slope = −0.46) and the acridinium and xanthylium cations (12 and 14; slope = −0.44).

rate–equilibrium correlations of Figs. 3–5. Four groups of cations, lying on different but approximately parallel correlation lines, appear to be indicated in Fig. 3 (log k_{OH} vs pK_{R^+}) and Fig. 4 (log k_2 vs pK_{R^+}). However, the relative reactivities (at constant pK_{R^+}) of these four groups of heterocyclic cations are quite different in each of these two figures: isoquinolinium > quinolinium > pyridinium > acridinium for log k_{OH} in Fig. 3; acridinium > quinolinium > isoquinolinium > pyridinium for log k_2 in Fig. 4. Neither of these individual reactivity orders is exactly the same as that indicated by the rate–rate correlations in Fig. 2. However, the correlation of log (k_2/k_{OH}) vs pK_{R^+} (Fig. 5) does display four distinct correlation lines having the same order of group reactivities as that which is seen in Fig. 2.

The following points are noteworthy, and apply to each of Figs. 2–5:

(a) The π-isoelectronic acridinium (12) and xanthylium (14) cations appear to describe a correlation line that parallels the more extensive correlations of the other groups of reactant cations.

(b) The tropylium (13) cation appears to fit with the reactions at C-4 of the quinolinium cations. This may be fortuitous, but it should be of some predictive value for reactions of other substituted tropylium cations.

(c) The phenanthridinium cation (23) and C-2 reactions of the 3-bromoquinolinium cation (7′) are consistent with the data for isoquinolinium cations. However, the phthalazinium cations (21 and 22) show deviations from the isoquinolinium cations with which they are π-isoelectronic.

(d) Not unexpectedly, the 3,4-dihydroisoquinolinium cation (24) cannot be described by any of the correlations for the reactions of heteroaromatic cations.

The enhanced k_2/k_{OH} reactivity of the P4 cations has previously been demonstrated (*50*) for a more limited series of cations for which all data were extrapo-

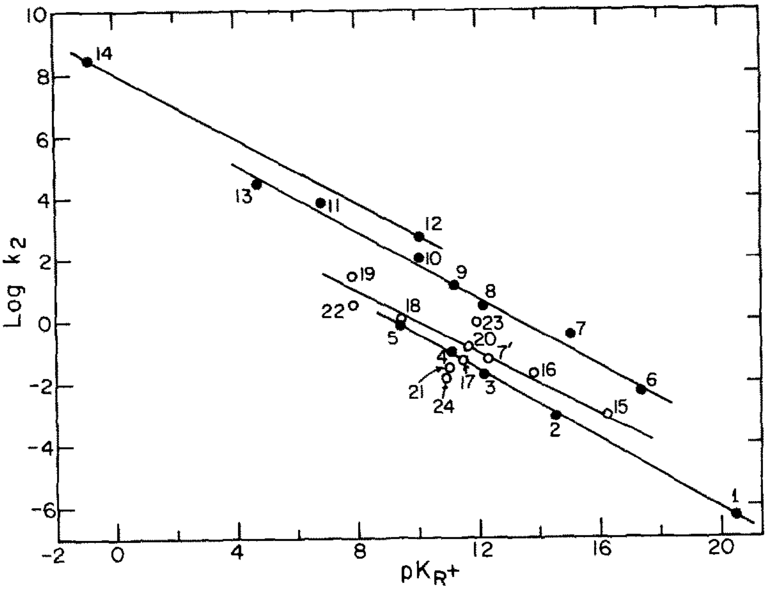

FIG. 4. Dependence of log k_2 upon pK_{R^+} for cations from Table 1. Lines (top to bottom) represent data for the acridinium and xanthylium cations (12 and 14; slope = −0.54), quinolinium cations (6–11; slope = −0.54), isoquinolinium cations (15–20; slope = −0.49) and pyridinium cations (1–5; slope = −0.57).

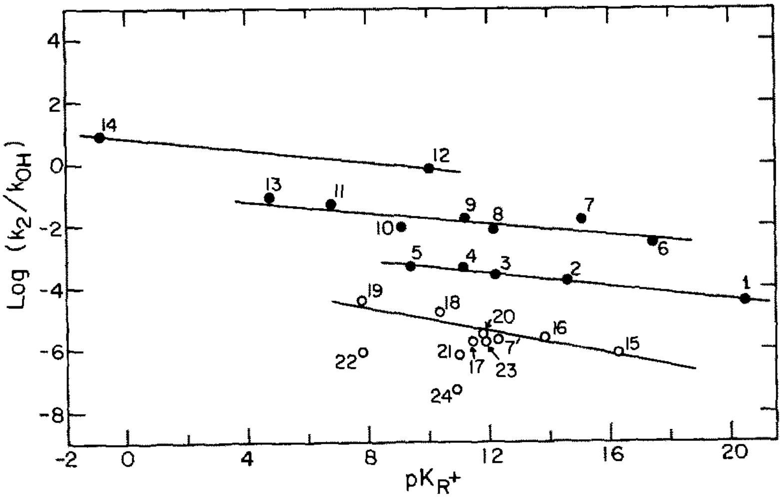

FIG. 5. Dependence of log (k_2/k_{OH}) upon pK_{R^+} for cations from Table 1. Lines (top to bottom) represent data for acridinium and xanthylium cations (12 and 14; slope = −0.09), quinolinium cations (6–11; slope = −0.08), pyridinium cations (1–5; slope = −0.10) and isoquinolinium cations (15–20; slope = −0.19).

lated to $pK_{R^+} = 10.0$. In that work it was also noted that the k_2/k_{OH} ratio showed a significant increase with reactivity (k_2) within the Class P4 cations. A quantitative expression of the relative reactivities of the cation classes of Figs. 3, 4, and 5 is given in Table 2 by interpolation in each case at $pK_{R^+} = 10.0$. This latter value both represents the measured pK_{R^+} for the *N*-methyl acridinium cation (*66*) and is approximately the midpoint of the pK_{R^+} range of the acceptor cations for which data are currently available.

One feature of the relative reactivities that are deduced for acridinium, quinolinium, and pyridinium cations in Table 2 appears to be particularly noteworthy. Thus, the relative values of k_2 that have been deduced by interpolation in Fig. 2 at constant k_{OH} (550 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$) are essentially identical to the relative k_2/k_{OH} ratios for cations of $pK_{R^+} = 10.0$. These 1 : 40 : 2000 ratios that are observed for pyridinium : quinolinium : acridinium cations seem to be particulary significant, since for the cations of $pK_{R^+} = 10.0$, the individual k_2 and k_{OH} rate constants do not show these same relative ratios. This point is addressed further at a much later point in the following discussion. It should be noted, however, that the ~1000-fold greater reactivity of 1-benzyl-1,4-dihydronicotinamide than of 10-methyl-9,10-dihydroacridine as a reducing agent for these heteroaromatic cations is essentially invariant over a 10^8-fold change in reactivity of these cationic acceptors (*52*). Similar observations, although they are much less extensive, have been made for the reduction of these cations by other substituted 1,4-dihydropyridines (*47*) and also by 5-methyl-5,6-dihydrophenanthridine (*51*). Thus, the general observations enunciated above upon the reactivity of 1-benzyl-1,4-dihydronicotinamide toward cationic acceptors can probably be generalized to other related reducing agents derived from 1,4-dihydropyridine.

SINGLE ELECTRON TRANSFER PROCESSES

The dramatic difference between the two classes of cations in Fig. 1 makes it clear that reactivity toward a nucleophile such as hydroxide ion does not allow a unique rationalization of the reactivities of all cations toward reduction by 1,4-dihydronicotinamides and related reducing agents. Correlations of k_2 with other properties of these aromatic cations have therefore been sought. Two quantitative properties, that are available for a number of these cations, are their electron affinities (EA) and their half-wave polarographic reduction potentials ($E_{1/2}$). The available EA and $E_{1/2}$ data for these cations are included in Table 1. The dependences of log k_2 upon each of EA and $E_{1/2}$ are indicated in Fig. 6 and 7, respectively. These two figures describe convincing linear correlations for k_2. General correlations of log k_{OH} with either of these two parameters are quite scattered, although cations that have been identified above as Class P4 cations do show reasonable correlations of log k_{OH} with their one-electron acceptor properties. Least-squares fitting of the log k_2 data in these two figures gives Eqs. [5] and [6]. These two equations include data for both P4 and (a limited number of) P2 cations.

$$\log k_2 = 8.7(\pm 0.3)\ \mathrm{EA} - 50.6(\pm 0.5) \qquad (r = 0.995) \qquad [5]$$

$$\log k_2 = 9.8(\pm 0.5)\ E_{1/2} + 6.3(\pm 0.7) \qquad (r = 0.986) \qquad [6]$$

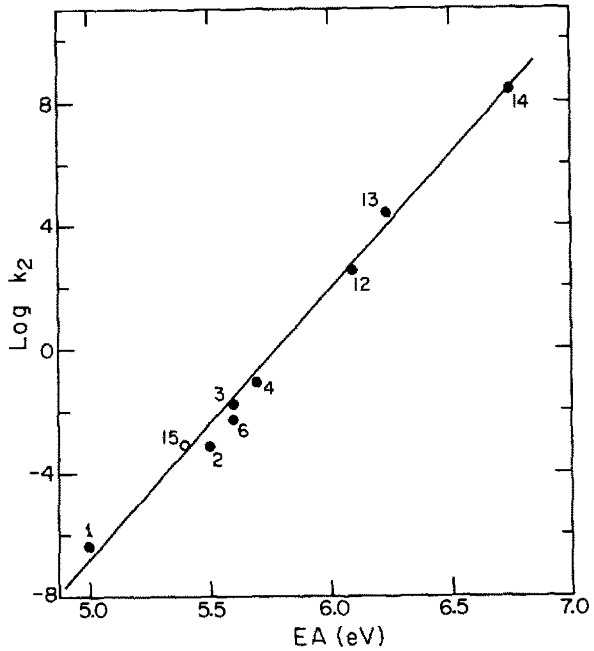

FIG. 6. Dependence of log k_2 upon the electron affinity (EA) of the cations in Table 1. The correlation line is Eq. [5].

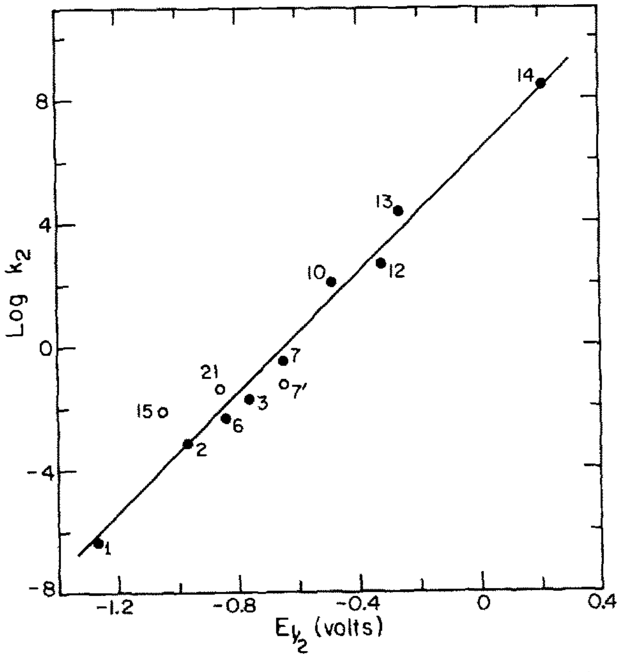

FIG. 7. Dependence of log k_2 upon the one-electron reduction potentials of the cations in Table 1. The correlation line is Eq. [6].

Although the number of cations that can be presently included is limited by the availability of EA and $E_{1/2}$ data, Eqs. [5] and [6] are clearly more accurate general descriptors of the variation of k_2 with acceptor cation structure than is the attempted correlation of k_2 with k_{OH} in Fig. 1. Figures 6 and 7 represent correlations of log k_2 with one-electron acceptor properties of the cations under study. These correlations are remarkably reminiscent of the analogous correlations that have been reported (*79*, *80*) for the rates of the one-electron reductions of a wide range of aromatic cations, including tropylium ions and the *N*-methylacridinium cation, by the Cr(II) ion. The slope of the correlation line in Fig. 7 is similar to that found[1] for Cr(II) reduction of such cations.

It is well established (*79*, *80*) that electron affinities and reduction potentials correlate with one another for a series of electron acceptors, and that these parameters may also be correlated with the charge-transfer band energies for the interaction of a common donor with the same series of acceptors (*80–82*). We have also recently noted relationships between the rates of 1,4-dihydronicotinamide reduction of many of the cations in Table 1 and the charge-transfer maxima for their interaction with N,N-dimethyl-*p*-toluidine, and also with the equilibrium constants for charge-transfer complex formation (*61*). All of the above observations, and in particular the similarity between Figs. 6 and 7 and the analogous Cr(II) reductions of such cations (*79*, *80*), therefore point to the possible importance of a contribution from an SET process in these reductions of heteroaromatic cations by 1,4-dihydronicotinamides.

The ability of 1,4-dihydronicotinamide derivatives to act as one-electron donors has been definitively established with oxidants such as ferricyanide ion (*57*, *83*, *84*), ferrocenium cations (*22*, *27*), and a variety of organic radicals (*22*). On the basis of studies using such oxidants, Miller and co-workers (*22*) have concluded that "only very powerful one-electron oxidants will be able to oxidize NADH via a mechanistic pathway involving one electron transfer." Marcus theory allows the prediction of the rate constants for related 1e$^-$ transfer processes, and thus the maximum rate constants for an oxidation in which 1e$^-$ transfer occurs from a 1,4-dihydronicotinamide to the oxidant species. Such considerations have indicated that the oxidation of quinones by NADH occurs 10^4-fold to 10^6-fold faster than can be accounted for by an initial electron transfer from the donor to the quinone oxidant. Similar considerations suggest that the experimentally observed second-order rate constants for the reduction of the *N*-methyl acridinium cation and of the *N*-propyl nicotinamide cation by NADH are greater by 10^7-fold and 10^{17}-fold, respectively, than can be accounted for by single-electron transfer from NADH to these cations.

The preceding ideas are summarized schematically in Fig. 8, using the data of Miller and co-workers (*22*). The three lines in this figure suggest correlations for (A) organic radicals, ferricyanide ion, and ferrocenium cations, (B) organic radicals and quinones, and (C) organic radicals and the two heteroaromatic cations. It

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[1] The slope (9.8) of the correlation in Eq. [6] can be compared with a slope of 8.7 which can be calculated for log k_2 vs E (=reduction potential) for assorted aromatic cations reaction with Cr(II) (*79*) and a slope of 9.7 for an extensive range of substituted tropylium cations and several cyclopropenylium cations reacting with Cr(II) (*80*).

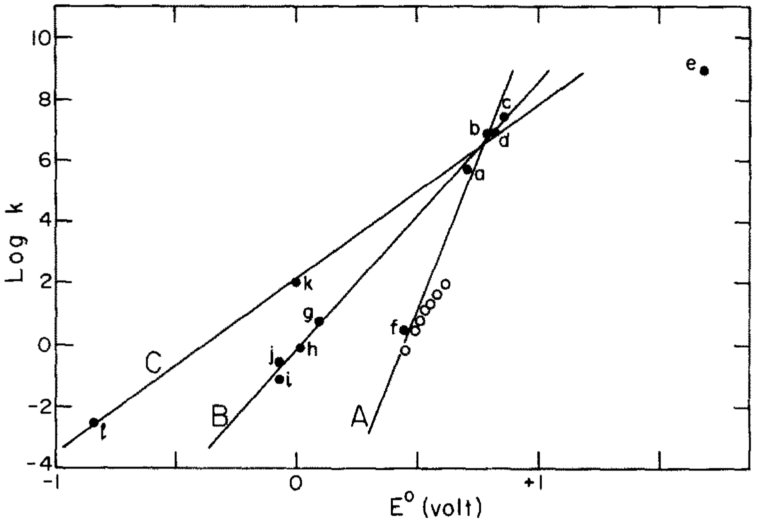


FIG. 8. Dependence of the second-order rate constants for the oxidation of NADH by various oxidants upon the one-electron oxidation potentials of these oxidants. All data are taken from Ref. (*22*). Oxidants are: radical cations (a, b, and c), *m*-benzosemiquinone (d), Br^-(e), ferricyanide ion (f), quinones (g–j), *N*-methyl acridinium cation (k), *N*-propyl nicotinamide cation (l). Various substituted ferrocenium cations are indicated by (o). Lines A, B, and C are discussed in the text.

is rather sobering to note that each of these three lines, individually, might be taken as acceptable linear free energy relationships between the second-order rate constants for the reduction of these oxidants by NADH and their one-electron reduction potentials. The lower line (A) represents those cases for which rate-limiting electron transfer has been definitively established, and this line also represents the predicted rates of electron transfer for oxidants of a given $1e^-$ reduction potential. On this basis it is quite clear that quinones and the two nitrogen heteroaromatic cations must be concluded to react with NADH by a mechanism which does not involve the transfer of a single electron in a discrete step. Such considerations also indicate that correlations such as those that are presented in Fig. 6 and 7 should not be taken as "proof" for single-electron transfer in the reductions of these cations by 1-benzyl-1,4-dihydronicotinamides.

Further evidence of the care that is necessary in the interpretation of correlations of rate constants for "hydride" transfer with one-electron acceptor properties of the hydride acceptor species can be found in the observation (*57*) of a clean linear correlation between the rate constants for ferricyanide ion oxidation of 1,4-dihydropyridines and 1,4-dihydroquinolines, and the rate constants for the reduction of the *N*-methyl acridinium cation by these same reductants. This relationship holds despite the fact that the argument in the previous paragraph indicates that the latter reactions are unlikely to involve a discrete electron transfer from the dihydropyridine derivative to the acridinium cation. Interestingly, ferricyanide ion oxidizes 10-methyl-9,10-dihydroacridine (k_2 = 2.0 M^{-1} s^{-1} in 20% CH_3CN–80% H_2O at 30°C (*85*)) under anaerobic conditions slightly faster than it oxidizes 1-benzyl-1,4-dihydronicotinamide (k_2 = 1.36 M^{-1} s^{-1} (*57*)), and this is the only known oxidant for which the relative rates of oxidation of these two substrates deviate significantly from ~1000 : 1 in favor of the dihydronicotinamide (*52*).

The matter of distinguishing between nucleophilic (hydride) attack and SET processes as mechanisms for the reduction of heteroaromatic cations is further complicated by the observation of clean correlations between equilibrium constants for nucleophilic addition and $1e^-$ reduction potentials and related one-electron transfer processes in some instances (*86*). The pK_{R^+} values of Table 1 also show general systematic trends with both EA and $E_{1/2}$, although quantitative correlations are not particularly precise. Such relationships are presumably a reflection of the fact that the two processes, involving either the addition of an anionic nucleophile or the transfer of an electron, both result in the same net change in electrical charge upon the acceptor species. Thus to a first approximation, to the extent that both nucleophilic attack and electron transfer are controlled by the same considerations of charge stabilization, such correlations are not unexpected.

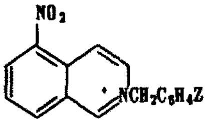
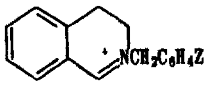
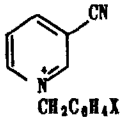
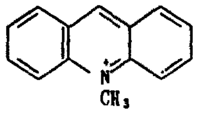
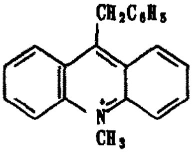
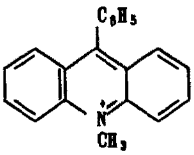
Since all steps in Schemes 1, 2, and 3 involve a change in electrical charge on the hydride donor and acceptor and/or the fission of a C–H bond, the structure of the rate-determining transition state can be probed through electronic substituent effects and primary deuterium kinetic isotope effects upon the rates of these reactions. Applications of these techniques to the reduction of isoquinolinium cations (*44*, *45*) and of 3,4-dihydroisoquinolinium cations (*46*) by 1,4-dihydronicotinamides lead to the clearcut conclusion that, for these two classes of heterocyclic cations, these reactions are examples of the direct hydride transfer of Scheme 1, with the migrating hydrogen bearing significant fractional negative charge and thus being quite hydridic in character. In the rate-determining transition state for each of these reductions, positive charge development upon the nicotinamide donor "gets ahead" of charge neutralization upon the cationic isoquinolinium or 3,4-dihydroisoquinolinium hydride acceptor. Quantitative data are presented in Table 3.

The above situation contrasts with that observed (*49*) in the reduction of nicotinonitrile cations by 1,4-dihydronicotinamides. In this case, transition state charge generation on the hydride donor exactly parallels charge neutralization on the hydride acceptor, and so the migrating hydrogen species bears no net fractional charge in the transition state. Pronounced substituent-dependent deuterium primary kinetic isotope effects are observed in the reduction of C-3-substituted pyridinium and quinolinium cations (*48*, *50*). In the latter case, these isotope effects have been shown (*48*) to be consistent with a "Westheimer dependence" (*87*) with an intrinsic barrier of 2.9 kcal/mol for hydride transfer. However, the fact that the kinetic control of the products of the 1,4-dihydronicotinamide reduction of these cations (*48*, *78*) has quite different regiospecificity than for the borohydride ion reduction of (*78*), or hydroxide ion addition to (*64*), these same cations suggests that the migrating hydrogen species might not have significant hydridic character in these reactions.

The 1,4-dihydronicotinamide reductions of pyridinium, quinolinium, and acridinium cations all formally give 1,4-dihydropyridines (i.e., attack γ to the cationic nitrogen atom) as the kinetically controlled products, whereas reductions of iso-

TABLE 3

Transition State Charges in the Reduction of Heterocyclic Cations by N-(Substituted Benzyl) 1,4-Dihydronicotinamides[a]

Reaction	Acceptor	*d*	*a*	*h*	k^H/k^D	Ref.
A		+0.82	+0.62	−0.44	6.6	(*44*)
B		+0.81	+0.52	−0.33	5.4	(*46*)
C		+0.67	+0.34	−0.01	2.7	(*49*)
D		+0.72			1.56	(*47*)
E		+0.97			2.7	(*47*)
F		+1.0			5.4	(*47*)

[a] In 20% acetonitrile–80% water, ionic strength 1.0, 25°C. k^H/k^D are for reduction by 1-benzyl-1,4-dihydronicotinamide and its 4,4-dideutero derivative. Related substituent and kinetic isotope effect data from other laboratories in other solvents may be found in Ref. (*17*, *57*, *93*, *94*, *125*, *126*, *127*).

quinolinium and phenanthridinium cations produce 1,2-dihydropyridine derivatives (from attack α to the cationic nitrogen atom). The rates of γ-attack in 1,4-dihydronicotinamide reductions are enhanced by up to 10^5-fold relative to the rates for α-attack when compared with the relative rates of nucleophilic attack at C-2 and C-4 in these heteroaromatic cations (*50*, *52*). This observation is most simply interpreted in terms of a pathway being available for the formation of 1,4-dihydropyridines that is more facile than the nucleophilic hydridic attack that has been established for the formation of a 1,2-dihydropyridine system in the reduction of isoquinolinium cations. In this context, Schemes 2 and 3 would then seem to represent the most likely possibilities for γ-attack rather than the direct hydride transfer of Scheme 1, which is only consistent with the established hydridic transition state for α-attack.

It should be noted that the deuterium primary kinetic isotope effects and substituent effects in the hydride donor that are observed for the reduction of acridinium cations by 1,4-dihydronicotinamides do seem to be consistent with the two-step sequence of Scheme 2 (e^-, $H^\cdot$) *(47)*. Such as interpretation is consistent with the known ready formation of acridinyl radicals by electron transfer to acridinium cations *(47, 88)*.

The following discussion attempts a rationalization of the apparent inconsistencies in the various mechanistic views that have been summarized in the foregoing discussion for these formal hydride transfer processes. These considerations involve an application of the More O'Ferrall–Jencks reaction coordinate diagrams *(89, 90)* that have become quite popular for the analysis of transition state structure in a variety of substitution, addition, and elimination reactions. An alternative use of such reaction coordinate diagrams has been reported by Kreevoy and Lee *(91)* in their studies of related hydride transfer reactions.

REACTION COORDINATES FOR HYDRIDE TRANSFER

Irrespective of reaction mechanism, the determination of the overall electron density distribution is an essential element in the complete description of the rate-determining transition state species for the formal hydride ion transfer between two heteroaromatic cations according to Eq. [1]. In the simplest terms, one may enquire as to what fraction of the formal unit charge change, which is required by Eq. [1] for both the donor and the acceptor species, has occurred when the transition state structure is reached. We will denote these charges as $+d$ and $+a$ for the donor and acceptor species, respectively, during the course of the reaction. If there is no accumulation of charge upon the migrating hydrogen species, then $d + a = 1$. If $(d + a) > 1$, then the location of significant excess electron density upon the migrating hydrogen species is indicated; i.e., significant "hydridic" character for the migrating hydrogen species. Similarly, if $(d + a) < 1$, then fractional positive charge, and consequently "protonic" character is implied for the migrating hydrogen species.

Such ideas may be conveniently described by reference to Fig. 9. The reactant and product species of Eq. [1] are denoted by the lower left and upper right corners, respectively. The lower right corner describes the limiting case of complete C–H bond breaking in the donor species before C–H bond formation begins in the acceptor species; i.e., the formal generation of a hydride ion intermediate species. The upper left corner also represents a limiting case of a free proton transfer between two neutral radical species. Note that this latter case implies a formal electron transfer for HD to A^+ in addition to the formation of a free proton as an intermediate species. The abscissa coordinate in Fig. 9 denotes the charge

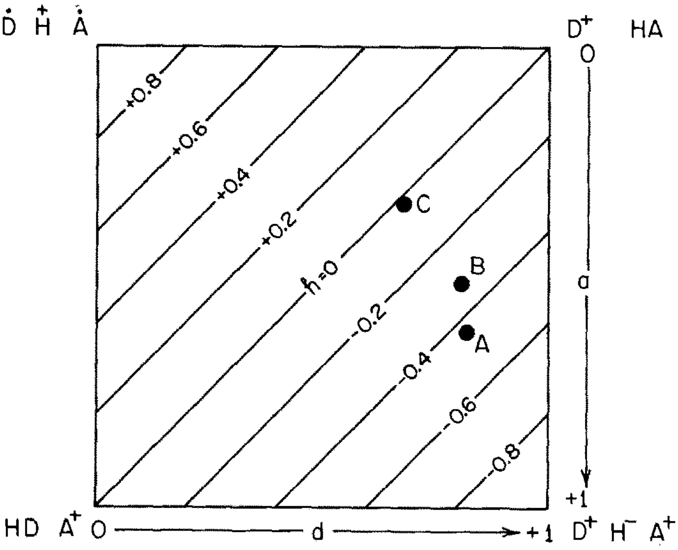


FIG. 9. Reaction coordinate diagram for hydride transfer according to Eq. [1]. Points A, B, and C represent the transition state species that are indicated in Table 3 for Reactions A, B, and C as determined by the charges a, d, and h.

on the donor species ($+d$), which varies from 0 at the start of the reaction (HD) to +1 (on D^+) when reaction is complete. Similarly, the ordinate in this figure represents the charge on the acceptor species; this charge varies from +1 on the reactant to 0 on the reduced acceptor (HA). Strictly, the ordinate is represented by $(1 - a)$, which varies from 0 to 1 as the reaction proceeds, and represents the fractional charge neutralization upon the acceptor species.

Any point within Fig. 9 can be represented by the coordinates $(d, (1 - a))$. With the restriction that $a + d + h = 1$ (where h is the fractional charge upon the migrating hydrogen species), the geometric properties of Fig. 9 then allow the description of h in terms of the lines of 45° slope that are shown in this figure. The value of h varies from -1 in the lower right corner to $+1$ in the upper left corner, with the direct diagonal from reactants to products being described by $h = 0$. Thus, any point lying below the $h = 0$ diagonal will represent a situation in which the development of cationic character upon the donor "gets ahead" of positive charge neutralization upon the acceptor, and therefore results in the development of excess electron density ($-1 < h < 0$; i.e., hydridic character) upon the migrating hydrogen species. Similarly any point above the $h = 0$ diagonal represents a situation in which "protonic character" ($0 < h < 1$) develops upon the migrating hydrogen species.

In principle, estimates of the values of $+a$ and $+d$ in the transition state species are experimentally accessible from studies of substituent effects in the acceptor and donor species, respectively, upon the reaction rates. The slope of a plot of log k_2 vs log K (where K is the equilibrium constant for hydride transfer from HD to A^+) should provide a reasonable estimate of the charge development (or neutralization) in the transition state species relative to the charge change which occurs upon the donor (or acceptor) species in the overall reaction. Independent studies of substituent effects in both the donor and the acceptor species should then provide coordinates (d, $(1 - a)$) which allow the location of the transition state species within Fig. 9.

Kreevoy and co-workers (*91–94*) have evaluated equilibrium constants for a number of examples of reactions according to Eq. [1] in a solvent consisting of 80% 2-propanol–20% water. In predominantly aqueous media, solubility considerations preclude the direct evaluation of most equilibrium constants for Eq. [1] (HA and HD are typically large neutral heterocyclic species with limited aqueous solubilities). We have therefore chosen to estimate the fractional charges, $+a$ and $+d$, upon the transition state species from comparisons of Hammett ρ values for k_2 with equilibrium ρ values for related reactions in which charge neutralization occurs (*44*, *46*, *49*). In particular, we have made use of ring-substituted benzylic groups as substituents upon heterocyclic ring-nitrogen atoms as convenient probes of electronic charge upon the nitrogen heterocyclic species. For instance, substituent effects upon the equilibrium constant for the formal hydride transfer from N-(substituted benzyl) 1,4-dihydronicotinamides to various acceptors have been modeled by analogous substituent effects upon the equilibrium constants for cyanide ion dissociation from N-(substituted benzyl) 4-cyano-1,4-dihydronicotinamides (*95*). Similarly, substituent effects upon the equilibrium constants for the reduction of N-(substituted benzyl) cations have been equated with substituent effects upon equilibria for the hydroxide ion addition to these same species (*46*, *70*). Equilibrium constants for this latter reaction, which is commonly referred to as pseudobase formation, are usually represented as pK_{R^+} values (*96*). Thus, the fractional charge ($+a$) upon the acceptor species in the transition state for reduction of a series of cationic acceptors by a common hydride donor species is estimated from the slope of a plot of log k_2 vs pK_{R^+}.

Table 3 includes data for three reactions that we have investigated in this way in our standard reaction medium (20% acetonitrile–80% water; ionic strength, 1.0). The coordinates of the transition state species (d, $(1 - a)$) for each of these reaction series are indicated by the corresponding letters (A–C) in Fig. 9. For reactions A (reduction of 5-nitroisoquinolinium cations by 1,4-dihydronicotinamides) and B (reduction of 3,4-dihydroisoquinolinium cations by 1,4-dihydronicotinamides), the hydridic nature of the migrating hydrogen species in the transition state is clearly established. Such an hydridic species would be expected to resemble other anionic nucleophiles in its selectivity toward various isoquinolinium cations. Indeed a distinct linear relationship has been noted (*45*) between log k_2 (for reduction by 1-benzyl-1,4-dihydronicotinamide) and log k_{OH} (for hydroxide ion addition) for a series of isoquinolinium cations over a 10^4-fold range in reactivity. Although more examples are required, we suggest that such hydridic transition states may be characteristic of the reduction of the P2 series of cations by 1,4-dihydropyridine derivatives. Such hydridic transition states are most simply reconciled with the direct hydride transfer process of Scheme 1.

Reaction C (the reduction of 3-cyanopyridiniun cations by 1,4-dihydronicotinamides) in Fig. 9 represents a case in which charge neutralization on the cationic acceptor in the transition state seems to match cationic charge generation on the neutral donor species (*49*). Thus, the migrating hydrogen species appears to be close to electrical neutrality ($h = 0$). In principle, this result could be interpreted in terms of any one of the Schemes 1, 2, or 3. We defer further consideration of this reaction at present, but take it up again below.

We have been unable to locate any further examples in the literature in which substituent effects upon *both* the donor and the acceptor species have been used in attempts to fully describe the charge distribution in rate-determining transition state species for hydride transfer. There are, however, numerous cases in which substituent effects on *either* the donor or the acceptor have been reported (*17, 57, 93, 94, 125, 126, 127*), along with primary kinetic isotope effects from comparisons of hydrogen transfer and the corresponding deuterium transfer process. Such kinetic isotope effects are, of course, another index of transition state structure, and in conjunction with substituent effects can be used to give further insight into reaction mechanism and rate-determining transition state structure.

Figure 10 shows an alternative dissection to that considered in Fig. 9 for the overall formal hydride transfer process. Whereas Fig. 9 concentrates purely upon electrical charge, Fig. 10 couples charge reorganization with kinetic isotope effects which at least approximately reflect the importance of C–H bond fission at the hydride donor in the rate-determining transition state species.

Again, the formal hydride transfer from reactants in the lower left to products in the upper right is dissected into two discrete processes in two different ways. The lower right corner represents the situation in which electron transfer from donor

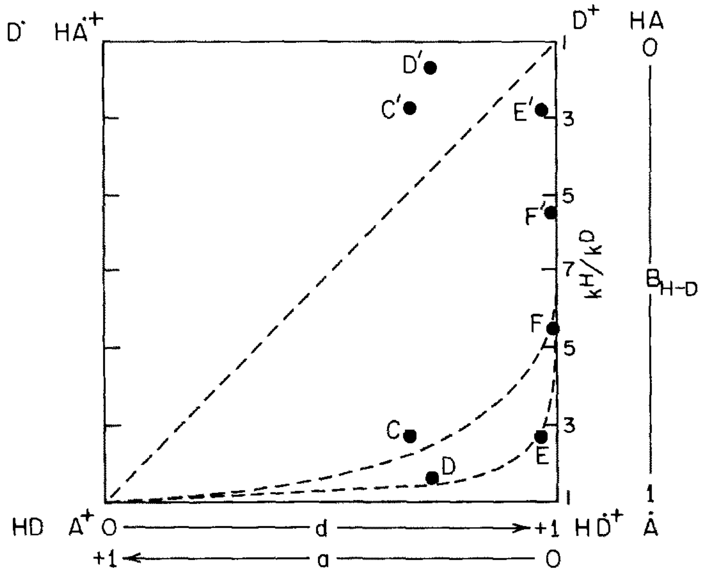


FIG. 10. Reaction coordinate diagram for hydride transfer according to Eq. [1]. Points C(C′), D (D′), E(E′), and F(F′) represent transition state species for the reactions C–F of Table 3. The alternative transition states that are possible for each of these reactions are discussed in the text.

to acceptor is complete. This in turn implies migration of positive charge from the acceptor (which becomes a neutral radical ($A^{\cdot}$)) to the donor species, and results in a formal radical cation ($HD^{\cdot +}$). Completion of the reaction via a route involving the lower right corner now involves a formal hydrogen atom transfer. The upper left corner represents the situation in which the formal hydrogen atom transfer process precedes electron transfer, in which case the intermediate species are represented as the radical cation of the protonated acceptor and a neutral donor radical species.

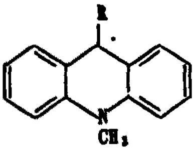
The abscissa in Fig. 10 represents positive charge development upon the donor species, or alternatively charge neutralization upon the cationic acceptor. Strictly speaking, Fig. 10 will only be applicable to those situations in which the migrating hydrogen atom is essentially electrically neutral ($h = 0$ and $d = (1 - a)$). We represent the ordinate axis by a primary kinetic isotope effect k^H/k^D which will be characteristic of the extent of C–H bond fission from the donor species. We assume a maximum isotope effect $k^H/k^D = 7$, and use a linear scale which shows k^H/k^D varying from 1 to 7 and then back to 1 consistent with the maximum predicted by Westheimer–Melander theory (*87*, *97*, *98*). While this ordinate axis represents the bond-order in the C–H bond in both the donor and the acceptor species, this scale will not be linear in bond-order, when it is represented as being linear in the experimentally measured k^H/k^D parameter. The direct hydrogen transfer from reactants to products via the diagonal broken line is not precluded; however, such a process must be characterized both by $h = 0$, and also have a transition state species which is characterized by appropriate coordinates (d, k^H/k^D) which lie upon this diagonal.

We first reconsider reaction C of Table 3, since this appears to be a clearcut case that fulfils the criteria that $d = (1 - a)$ and $h = 0$. For this reaction, $d = 0.67$ and $k^H/k^D = 2.7$. A disadvantage of the double-valued ordinate scale immediately becomes obvious, since the coordinates (0.67, 2.7) for the transition state species are consistent with either of the locations C or C′ in Fig. 10. Location C suggests a transition state in which electron transfer from the donor is "ahead" of C–H bond fission in HD; in terms of electrical charge the transition state appears product-like, whereas in terms of hydrogen transfer, the transition state appears reactant-like. For location C′, both charge transfer and C–H bond breaking are well advanced in the transition state species, and both indices suggest a product-like transition state structure. Whereas C suggests a transition state which has a structure containing significant features of the dihydronicotinamide radical cation ($HD^{\cdot +}$) and neutral nicotinonitrile radical ($A^{\cdot}$) species, C′ actually appears to be structurally closer to the nicotinamide cation (D^+) and 1,4-dihydronicotinonitrile (HA) product species than it is to either of the formal radical species of the upper left or lower right corners of this figure.

On the basis of the data that are currently available, there seems to be no simple way of establishing a preference for either C or C′ as a more likely representation of the transition state species. It should be noted that the thermodynamics of reaction C favor the nicotinamide cation and 1,4-dihydronicotinonitrile as the product species (D^+ and HA of Fig. 10) and this could be interpreted in terms of a lower energy for C′ than for C. However, if this preference is ascribed to the greater destabilization of the cationic species by a 3-cyano substituent than by a 3-aminocarbonyl substituent, then a similar effect might also be expected to operate in the radical cation species. In the current context, this would suggest that the 1,4-dihydronicotinamide radical cation ($HD^{\cdot +}$) would be more stable than the 1,4-dihydronicotinonitrile radical cation ($HA^{\cdot +}$). While such a situation would appear to favor C rather than C′, these radical species are of much higher energy than the stable reactant and product species, and consequently this effect may not be sufficient to tilt the three-dimensional energy surface in such a way as to produce a lower energy pathway via C than via C′.

Reactions D, E, and F of Table 3 represent the reduction of C-9-substituted 10-methylacridinium cations by 1-benzyl-1,4-dihydronicotinamides (*47*). Both the electron density (+*d*) on the donor and the primary kinetic isotope effect vary systematically in these reactions, and these empirical parameters may be used to locate the transition state species as D, E, and F (or D′, E′, and F′) on Fig. 10. In this case, D and D′ lie on opposite sides of the broken-line diagonal (similar to C and C′); however, E and F and E′ and F′ all lie below this diagonal. In principle, the ambiguity discussed above for C and C′ still remains for reaction D. However, it is clear for both reactions E and F that electron transfer is well ahead of C–H bond-breaking when the rate-determining transition state species is reached, although the extent of C–H bond-breaking is not unambiguously established by k^H/k^D. On this basis, it would seem reasonable to assume that location D, rather than D′, also most appropriately represents the transition state species for reaction D. Certainly, as discussed in more detail below, transition states D, E, and F are more readily rationalized in terms of a systematic variation in transition state structure with substitution at C-9 in the acridinium cation acceptors than are the transition states D′, E′, and F′. For this reason we will assume that D, E, and F are the appropriate transition state species for the reduction of acridinium cations by 1,4-dihydronicotinamides.

The occurrence of significant electron transfer in the reduction of these acridinium cations is certainly consistent with the well-known ability of these cations to act as electron acceptors (*47*, *88*, *99*). The systematic variation of both +*d* and k^H/k^D in the reactions D, E, and F is also consistent with the expected increasing stability of radical species (**3**) in terms of the expected stabilization of R = H, $CH_2C_6H_5$, and C_6H_5 upon a radical center at C-9 of these species. It is important to note that the presence of **3** as a discrete reaction intermediate in these reactions is not established by these observations and should not be assumed. Although E and F appear to lie close to (or on) the right ordinate axis of Fig. 10, the reaction progress to these transition state locations does not necessarily proceed through the formal radical species in the lower right hand corner of this figure. The dotted



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lines for reactions E and F in Fig. 10 suggest approaches to transition states E and F which avoid the formal radical species, but which allow electron transfer to be significantly ahead of C–H bond-breaking at the energy maximum upon the reaction pathway.

The physical description of the trajectories that are indicated in Fig. 10 requires a rate-determining transition state species in which electron density transfer from the donor onto the acceptor cation has progressed more completely than is implied by the magnitude of the bond order between the migrating hydrogen species and the acceptor. In other words, in the formal transfer of the hydride ion in these reactions, electron density transfer "gets ahead" of the bond formation to the migration hydrogen species, so that these processes become somewhat uncoupled rather than being completely concerted phenomena. However, these two processes remain sufficiently coupled that discrete radical intermediates ($A^{\cdot}$ and $HD^{\cdot+}$) are not generated from a formal single electron transfer step in these reactions. A similar conclusion has been reached by Bethell and co-workers for the reactions of 9-arylfluorenyl cations with arylmethanes (*100*).

VALENCE BOND CONFIGURATION MIXING THEORY

A theoretical basis for the partial uncoupling of the electron transfer and hydrogen migration events can be found in the valence-bond configuration mixing (VBCM) model which has been developed by Shaik and Pross in recent years for the description of a wide variety of transition state phenomena in a broad range of chemical reactions (*33*, *101–105*). In particular, this model has been extensively applied to the description of the S_N2 process in terms of a single electron shift, without the intervention of intermediate radical species, rather than in terms of the more standard descriptions of such reactions in terms of two-electron bond formation and bond fission processes (*33*, *102*, *103*, *106*). Pross and Shaik have been particularly careful to stress that a single electron *shift* between valence bond contributors to the electronic structure of a transition state species should not be confused with a single electron *transfer* which results in the formation of discrete radical species. The following discussion attempts a rationalization of the hydride transfer reaction of Eq. [1] in the context of the VBCM model. There have been several previous limited considerations of these reactions in terms of VBCM theory (*105*, *107*), but there does not appear to have been any previous comprehensive application of this model in the context of experimental data such as those that form the basis of Fig. 9 and 10.

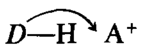
The configurations **A**–**F** form a basis set of valence bond contributors for the description of the progress of the hydride transfer process of Eq. [1]. The species **A** and **B** may be considered as the reactant configuration and the product configuration, respectively. Formally, these **A** and **B** configurations differ only in the shift of an electron from the donor (HD) to the acceptor (A^+). Starting with the reactant configuration, alternative one-electron shifts can also lead to the configurations **C** and **D**. These will be referred to as the hydridic configuration (**C**) and the protonic configuration (**D**), respectively, for obvious reasons. The configurations **E** and **F** are also related to the reactant configurations by one-electron shifts. By analogy with the above terminology for configurations **C** and **D**, configurations **E** and **F** may be referred to as atomic configurations, or radicaloid configurations, with the emphasis in the latter nomenclature being upon the presence of a hydrogen radical in **E** and **F** and not upon the radical nature of either the donor or the acceptor species.

$$\begin{array}{cc}
D\cdot\ \cdot H\ A^{+} & D^{+}\ H\cdot\ \cdot A \\
\mathbf{A} & \mathbf{B} \\[1em]
D^{+}\ H{:}^{-}\ A^{+} & D\cdot\ H^{+}\ \cdot A \\
\mathbf{C} & \mathbf{D} \\[1em]
D^{+}\ \cdot H\ \cdot A & D\cdot\ H\cdot\ A^{+} \\
\mathbf{E} & \mathbf{F}
\end{array}$$

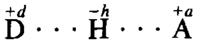
Progress along the reaction coordinate of Eq. [1] in a single-step reaction, without discrete intermediate species, will then be described in terms of the mixing of contributions from each of the valence bond contributors **A–F.** The particular mix of these contributors to the highest energy species on the reaction coordinate, i.e., the rate-determining transition state species, can be probed through the usual experimental studies of electronic substituent effects, kinetic isotope effects, solvent effects, etc., that one uses to gain insights into transition state structure.

Reductions of isoquinolinium and 3,4-dihydroisoquinolinium cations by 1,4-dihydronicotinamides have been established as involving the development of significant fractional negative charge upon the migrating hydrogen atom in the transition state (*44*, *46*). Such a situation is clearly readily represented in terms of the configurations **A**, **B**, and **C** being the major valence bond contributors along the reaction coordinate in these cases. Note that these reactions represent situations in which the development of cationic character upon the donor “gets ahead” of positive charge neutralization upon the acceptor species. This condition is consistent with the fact that of these three contributors (**A**, **B**, and **C**), two (**B** and **C**) bear formal positive charges upon the donor species, and two (**A** and **C**) also bear formal positive charges upon the acceptor species. Primary deuterium kinetic isotope effects indicate significant D–H bond fission in the transition states for these reactions, which is consistent with major contributions for **B** and **C**. The fractional negative charge upon the migrating hydrogen species in these reactions is of course rationalized in terms of the contribution from **C.**

Such examples of Eq. [1] in which “hydridic” character for the migrating hydrogen species is clearly established, could well be termed hydride transfer processes, and could conventionally be written in terms of the species **G** which implies a two-electron migration from the donor to the acceptor species. However, the VBCM description of this process in terms of the configurations **A**, **B**, and **C** emphasizes the fact that formally the reactant and product configurations differ only in terms of a one-electron shift. This apparent paradox of a formal two-electron process being represented in the VBCM model in terms of a one-electron shift has ben considered at length for S_N2 reactions *(33, 102, 103, 106)*, and will not be further explored here. Note that the conventional representation of the transition species as **G** does not explicitly indicate the development of excess electron density upon the migrating hydrogen species. The conventional representation of this charge development upon the migrating hydrogen species would be in terms of a structure such as **H**, which is in fact the result of mixing the configurations **A**, **B**, and **C**.



G



$\overset{+d}{D}\cdots\overset{-h}{H}\cdots\overset{+a}{A}$

H

Significant contributions from the configurations **D** and **E** are consistent with the situation in which significant electron density transfer onto the acceptor species precedes the formation of the H–A bond. Configurations **D** and **E** clearly imply a relationship between transition state stability and the one-electron acceptor properties of A^+. Thus the correlations of Fig. 6 and 7 may be interpreted in terms of significant contributions from **D** and **E**. Hence, we will now proceed upon the assumption that the configurations **A**–**F** may all make significant contributions to the electronic structures of the transition state species that are represented in Fig. 10. Since the relative weights of each of these contributors are unknown, much of the following discussion must necessarily be qualitative. However, in certain cases it will be possible to draw conclusions as to whether individual members of the basis set **A**–**F** are major, or only minor, contributing configurations to the structure of the transition state species.

In considering reactions D, E, and F of Table 3 and the corresponding transition states of Fig. 10, we note that one would predict the stability of the acridine radical species **3** to increase in the order $H < CH_2C_6H_5 < C_6H_5$. This should result in an increase, in this same order, of the relative weights of **D** and **E** to the transition state structure. Furthermore, substituent effects in the *N*-benzyl units of 1,4-dihydronicotinamide donors suggest that the development of transition state cationic charge ($+d$) upon the donor species is in this same order, and is essentially complete for the 9-phenyl derivative *(47)*. Taken together, these two observations suggest the increasing importance of configuration **E** (rather than configuration **D**, which does not imply cationic charge upon the donor species) to the structure of the transition state species. To the extent that this increased contribution from **E** is at the expense of the weighting from the reactant configuration **A**, this interpretation then also predicts an increase in D–H bond fission in the order $H < CH_2C_6H_5 < C_6H_5$ in the rate-determining transition state species. The increase in the primary kinetic isotope effects (k^H/k^D) in this same direction is quite consistent with this interpretation.

The notion of a highly variable transition state structure in these formal hydride transfer reactions finds support in the significant variations in k^H/k^D that have been observed as a function of substitution in a cationic acceptor species, as a function of substitution in the hydride donor species, and also as a function of solvent.

TABLE 4

Primary Kinetic Isotope Effects for Reduction of Quinolinium and Pyridinium Cations[a]

Cation	Substituent	pK_{R^+}	k_2^H(M^{-1} s^{-1})	k_2^H/k_2^D
Quinolinium[b]	H	17.4	0.005	4.2
	3-Br	15.1	0.38	5.8
	3-$CONH_2$	12.18	2.8	5.2
	3-CO_2CH_3	11.28	14.3	4.0
	3-CN	9.06	121	1.8
	3-NO_2	6.82	6500	1.5
Pyridinium[c]	3-$CONH_2$[d]	14.6	0.002	6.2
	3-$COCH_3$[e]	13.4	0.0077	3.7
	3-CN[f]	12.0	0.018	3.0
	3-NO_2[g]	9.42	0.72	2.0

[a] For reduction by 1-benzyl-1,4-dihydronicotinamide and its 4,4-dideutero derivative in 20% acetonitrile–80% water, ionic strength 1.0, at 25°C.

[b] For reaction at C-4 of the *N*-methyl cations; pK_{R^+} data are from Ref. (*64*); rate data are from Ref. (*48*).

[c] For reaction at C-4 of the *N*-methyl cations unless indicated otherwise; pK_{R^+} data are from Ref. (*63*).

[d] For the *N*-benzyl cation; rate data are in 25% acetonitrile–75% water at 40°C (*11*).

[e] Unpublished results by J. L. Bolton and J. W. Bunting.

[f] Rate data from Ref. (*49*).

[g] Rate data from Ref. (*50*).

Substituent effects upon k^H/k^D for the reduction of C-3-substituted *N*-methyl quinolinium and pyridinium cations are summarized in Table 4. A similar variation in primary kinetic isotope effect with equilibrium constant has been observed by Kreevoy and co-workers (*108*) for the reduction of N-substituted and C-3-substituted quinolinium cations by 5-methyl-5,6-dihydrophenanthridine and its 6,6-dideutero derivative. These data can be described in terms of the Hammond Postulate, with increasingly favorable thermodynamics for hydride transfer leading to earlier (more reactant-like) transition states and therefore less C–H bond fission in the donor (HD). In terms of the VBCM model, this result implies more important contributions to the transition state species from the reactant configuration (**A**) for more thermodynamically favorable reactions.

Solvent-dependent k^H/k^D ratios have been reported for these formal hydride transfer processes (*21*, *109*). For instance, for the reduction of the *N*-methyl acridinium cation by 1-benzyl-1,4-dihydronicotinamide, k^H/k^D varies from 4.1 to 4.6 in acetonitrile (*21*, *117*) to 1.56 in 20% CH_3CN–80% H_2O (*47*) and 1.4 in methanol (*62*). Again, a transition state structure that is quite sensitive to the environment is indicated. Within the VCBM model, significant solvent dependence of the relative weights from the various basis set configurations is indicated.

The different correlation lines that are required for pyridinium, quinolinium, isoquinolinium, acridinium cations, etc. as acceptor species (Fig. 2, 4, and 5) are also consistent with considerable variation between these acceptor families in the contributions from the various VBCM basis set configurations to the transition state structure. In view of the known variation in the efficiency of charge-transfer complexation for these families of cations (*61*), one suspects that the configurations **D** and **E** are most important in establishing these different correlation lines for these different classes of acceptor cations. The clear indication for "hydridic" character that has been established for the migrating hydrogen species in the transition state for the reduction of Class P2 cations is indicative of an important contribution from configuration **C**. However, it should be noted that excess electron density on the migrating hydrogen species, although less than that found for isoquinolinium cations, has also been diagnosed for the reduction of quinolinium cations by 10-methyl-9,10-dihydroacridine (*91*). Thus, configuration **C** may also be important for these members of the Class P4 cations.

The overall general picture that emerges from the reaction coordinate analyses of Figs. 9 and 10, and also out of the application of the VBCM model to the hydride transfer reactions of Eq. [1], is one of a highly variable transition state structure within a single-step reaction mechanism for these formal hydride transfer processes. These analyses all point to the merging of the formal SET mechanisms of Schemes 1–3 into a unified variable transition state structure. While there are examples of the oxidation of 1,4-dihydronicotinamides via SET mechanisms by reagents such as ferricyanide ion, it seems clear that a variable transition state model most readily accounts for all experimental data for the hydride transfer reactions between heteroaromatic cations in Eq. [1].

It is important to recognize that the view which one obtains of the rate-determining transition state species, and of the possible presence of discrete intermediate species, is limited by the method of observation, e.g., substituent effects in the donor, substituent effects in the acceptor, kinetic isotope effects, solvent effects, etc. A complete description of the structure of the transition state species can only be obtained as a result of a comprehensive investigation of all significant reaction variables. Such highly variable transition state structures contain the potential for imbalances in electron density distribution of the type which are now widely recognized for the deprotonation of carbon acids, nucleophilic additions to activated olefins, base-catalyzed elimination reactions, etc. (*110–114*). A particular case of such an imbalance is seen in the lag of the electron density transfer into isoquinolinium cations from 1,4-dihydronicotinamides as a result of the development of significant fractional negative charge upon the migrating hydrogen species (*44*). A further example is seen in the imbalance between electron transfer to the acridinium cation acceptors and the kinetic isotope effects which are the basis of the analysis in Fig. 10. It may be expected that many more such examples of imbalanced transition states will come to light as more comprehensive applications are made of all the experimental criteria that one may use to probe the structure of the transition state species in individual reactions.

RELATED STUDIES

This discussion would be incomplete without some consideration of the relationship between our own studies and those which have been proceeding concurrently in Kreevoy's laboratory (*78*, *91–94*, *108*, *109*, *115*, *116*). Kreevoy and coworkers have investigated hydride transfer reactions between various heterocyclic cations in 80% 2-propanol–20% water as the reaction medium, and have reported both rate constants and equilibrium constants for approximately 40 examples of such equilibrations according to Eq. [7] (compare Eq. [1]).

$$A_i^+ + A_jH \overset{K_H}{\rightleftharpoons} A_iH + A_j^+ \qquad [7]$$

These studies were originally designed to test the applicability of the Marcus relationship to hydride transfer processes (*91–94*), and more recently, to examine the possibility of tunneling phenomena in such hydride transfers via deuterium kinetic isotope effects (*108*, *115*, *116*). To these ends, these studies have employed various substituted 1,4-dihydropyridines, 1,4-dihydroquinolines, 9,10-dihydroacridines, and 5,6-dihydrophenanthridines as hydride donors toward the corresponding pyridinium, quinolinium, acridinium, and phenanthridinium cations. For six hydride transfers which are common to these latter studies in 80% 2-propanol–20% water and our own work in 20% acetonitrile–80% water, the second-order rate constants are always smaller (by factors varying between two- and eight-fold) in the less aqueous solvent. This observation is consistent with numerous reports of a decrease in reaction rate for such hydride transfer processes upon a decrease in the solvent polarity (*7*, *52*, *109*, *117–119*).

Rate–equilibrium correlations were found to be approximately linear over a broad range of reactivity (*92*, *94*), although in general, these relationships show considerable experimental scatter, presumably due to specific donor–acceptor interactions which complicate these studies as a result of the relatively heterogeneous set of mono-, bi-, and tricyclic donors and acceptors that are included. As expected, such Brønsted relationships are more clearcut when limited to reactants which are closely related in structure (*91*). Remote substituent effects in the C-4 reduction of a series of N-(substituted benzyl) 3-cyanoquinolinium cations by 10-methyl-9,10-dihydroacridine indicated a loose transition state with the development of significant excess electron density upon the migrating hydrogen atom (*91*), although the hydridic character of this migrating hydrogen appears to be less pronounced than that which we have deduced for the reduction of isoquinolinium and 3,4-dihydroisoquinolinium cations by 1,4-dihydronicotinamides (*44*, *46*).

The application of Marcus theory to these reactions has lead to the measurement of rate constants for at least 11 examples of symmetrical (i.e., degenerate) hydride transfers (*92*, *94*). Rather than being constant, as is required if these data are to be treated within Marcus theory by a single intrinsic barrier, rate constants for such symmetrical hydride transfers vary by approximately 250-fold, and in general, increase in the order pyridines < quinolines < phenanthridines < acridines. It should be noted that there are also less pronounced variations in the rate constants for symmetrical hydride transfers within the variously substituted pyridine (21-fold range) and quinoline derivatives.

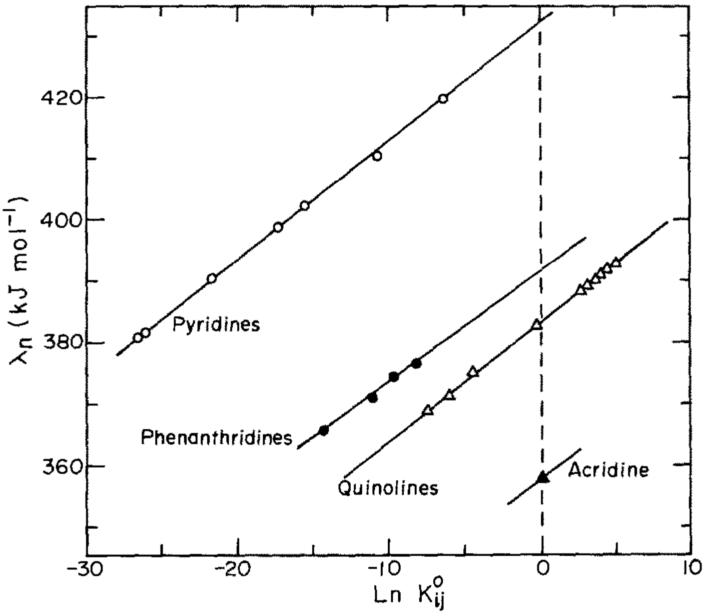


FIG. 11. Dependence of the calculated intrinsic barrier (λ_n) upon the equilibrium constant for hydride transfer to the *N*-methyl acridinium cation from various 1,4-dihydropyridine, 1,4-dihydroquinoline, and 5,6-dihydrophenanthridine derivatives. All data are from Ref. (*94*).

It has been concluded (*94*) that a structure-sensitive intrinsic barrier is required, although the quantitative evaluation of these barriers ultimately requires knowledge of the experimentally inaccessible work terms that are necessary for a complete Marcus analysis. However, the relative values for such structure-sensitive intrinsic barriers are independent of the specific values assigned to these work terms, provided that such work terms are themselves assumed to be relatively structure insensitive. Figure 11 reproduces one set of such intrinsic barriers which have been evaluated by Kreevoy and co-workers (*94*). Note the requirement for separate correlation lines for pyridines, phenanthridines, quinolines, and acridines which is reminiscent of the situation that is apparent in Fig. 2, 4, and 5. Furthermore, one may use the interpolated intrinsic barriers at $K_H(=K_{ij}^0) = 1$, to calculate the rate constants for the symmetrical transfer reactions in each of these heterocyclic ring systems (Table 5). Amazingly, the relative reactivities that are obtained from such a sophisticated analysis based in Marcus theory are in quite reasonable quantitative agreement for the pyridine, quinoline, and acridine ring systems with the relative reactivities that are deduced in our own studies from direct comparisons of the rates of the 1,4-dihydronicotinamide reduction and hydroxide ion addition reactions for these same heterocyclic ring systems (compare Tables 2 and 5).

To a first approximation, one might expect that the equilibrium constants (K_H) for hydride transfer between two heterocyclic cations could reasonably be modeled by the equilibrium (Eq. [8]) for the formal hydroxide ion transfer between

TABLE 5

Relative Reactivities of Heteroaromatic Cations in Hydride Transfer Reactions

	Acridinium	Quinolinium	Pyridinium
From intrinsic barriers at $K^0_{ij} = 1$ in Fig. 11[a]			
	1900	130	1
From $\Delta pK_{R^+} = 0$ in Fig. 12			
	4000	300	1
From $\Delta pK_{R^+} = 0$ in Fig. 13			
	3000	500	1

[a] From data in Table II of Ref. (*94*).

these same cations. Values of K_{OH} as defined in Eq. [8] can be readily calculated from the individual pK_{R^+} values for pseudobase formation at the same site at which reduction occurs in each cation; i.e., $\log K_{OH} = \Delta pK_{R^+}$.

$$A_i^+ + A_jOH \overset{K_{OH}}{\rightleftharpoons} A_iOH + A_j^+ \qquad [8]$$

Most of the experimental K_H values for hydride transfers in 80% 2-propanol–20% water are considerably larger (as much as 10^5-fold greater in some cases) than predicted for K_{OH} from pK_{R^+} values in aqueous solution. It should be noted that these differences cannot merely be ascribed to a solvent effect, since apparent pK_{R^+} values in 80% 2-propanol–20% water are almost uniformly 2.3 units smaller than the corresponding values measured in aqueous solution, and thus ΔpK_{R^+} values are essentially solvent independent. Figure 12 (for a common acceptor, the 10-methylacridinium cation, reacting with a variety of hydride donors) and Fig. 13 (for 5,6-dihydrophenanthridines reacting with a variety of cationic acceptors) show that there is a systematic relationship, or more accurately, a series of systematic relationships, between the experimentally measured K_H and the calculated K_{OH}. In all cases pyridines and phenanthridines appear to share a common correlation line, irrespective of whether the cationic species are acting as hydride acceptors or their dihydro-derivatives are acting as hydride donors. It is not clear at this time whether this correspondence of data for pyridine and phenanthridine derivatives is meaningful or accidental. In view of the distinction which was drawn above between Class P2 and Class P4 cations, it seems more likely that the coincidental data for these two classes of derivatives is fortuitous.

It is clear that quite different correlation lines are required in Figs. 12 and 13 for dihydropyridines (and dihydrophenanthridines), dihydroquinolines, and dihydroacridines acting as hydride donors, and also for acridinium, quinolinium, and pyridinium cations as the acceptor species. These results, which represent correlations between equilibrium constants, then strongly suggest that the similar differentiations between these classes of cationic acceptors that are apparent in the rate–rate correlations of Fig. 2, and the rate–equilibrium correlations of Figs. 4 and 5, are not confined to specific transition state phenomena. The relative K_H at

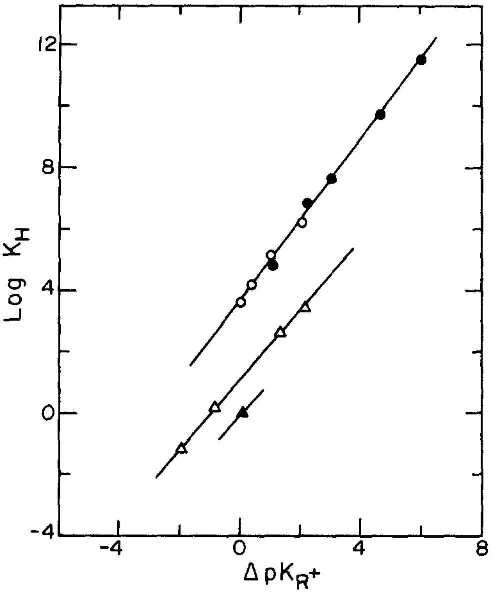


FIG. 12. Dependence of log K_H upon ΔpK_{R^+} for hydride transfer from 1,4-dihydropyridines (●), 5,6-dihydrophenanthridines (○), 1,4-dihydroquinolines (△), and 10-methyl-9,10-dihydroacridine (▲) to the *N*-methyl acridinium cation. All log K_H data are from Ref. *(94)*; pK_{R^+} are for aqueous solution.

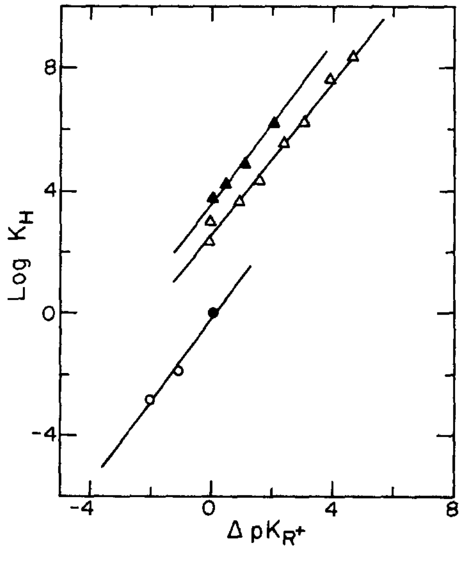


FIG. 13. Dependence of log K_H upon ΔpK_{R^+} for hydride transfer from 5,6-dihydrophenanthridines to acridinium cations (▲), quinolinium cations (△), pyridinium cations (○), and the *N*-methyl phenanthridinium cation (●). All log K_H data are from Ref. *(94)* pK_{R^+} are for aqueous solution.

$\Delta pK_{R^+} = 0$ in Figs. 12 and 13 (see Table 5) are in the same order as reported in Table 2. Furthermore, the fact that this differentiation between acceptor classes is now also apparent in these correlations between equilibrium constants indicates that the data of Table 2 and Figs. 2 and 5 cannot simply be ascribed to hydroxide ion being a poor kinetic model for the migrating hydride species.

These data suggest that there are important interactions between the cations and their dihydro-derivatives which are not included in the covalent bonding changes which are represented by comparisons of K_H and K_{OH}. Kinetic saturation effects, consistent with 1 : 1 complexation between donor and acceptor, are sometimes observable in these systems (*44*, *45*, *48*, *51*), and spectral data are available for charge-transfer complexation between a 1,4-dihydronicotinamide and an acridinium cation (*62*). The ability of heterocyclic cations to act as charge-transfer acceptors toward a common donor is well established as being: acridinium > quinolinium > pyridinium (*61*). The overall circumstantial evidence suggests that the equilibria of Eq. [7] may actually be complicated by noncovalent interactions between A_i^+ and A_jH and/or A_j^+ and A_iH. The greater than unit slopes indicated by the correlation lines in Figs. 12 and 13 may also be a clue to the presence of such complex species. Whereas pK_{R^+} values (and hence K_{OH}) are measured in dilute (~0.1 mM) solutions of the heterocyclic species, K_H is evaluated from the ratio of forward and reverse rate constants in solutions containing large excesses of one of the components of the final equilibrium mixture (*92*, *94*). Careful spectroscopic studies of selected reactant mixtures, and especially of the species that are present in solutions undergoing degenerate hydride transfer processes, may prove to be fruitful probes of this problem, and may provide more definitive evidence for the charge-transfer species which have often been indirectly inferred as intermediates in the hydride transfer reactions of Eqs. [1] and [7] (*61*, *94*, *124*).

Our expectation in the above discussion, that K_H may be reasonably modelled by K_{OH}, is similar to the approach that was used by Breslow and coworkers (*128*, *129*) in the evaluation of the thermodynamic cycles that form the basis of their studies of the acidities of very weak carbon acids. Essentially, such comparisons assume a linear free energy relationship between the heterolytic cleavages of C—H and C—O bonds upon the variation in the molecular structure which incorporates the sp^3-hybridized carbon atom in these bonds. However, a caveat with regards to such assumptions, can be found in the recent conclusions from Arnett's laboratory (*130*, *131*) which suggest that the C—O bond may be a relatively poor model for the C—C bond in linear free energy relationships. It is not clear to what extent these latter conclusions may be influenced by comparisons of data for the heterolysis of C—O bonds in aqueous solution with data for the heterolysis of C—C bonds in sulfolane solutions. It is also not clear to what extent this observation can be extended to comparisons of C—O and C—H bonds, although dramatic solvent changes have been avoided in the comparisons which we have used, since all data are for either aqueous or aqueous organic media. Nevertheless, there can be no doubt that the direct measurement of K_H, as practised by Kreevoy and coworkers, is to be preferred whenever this equilibrium constant is directly accessible, although as indicated above, caution must be exercised since such K_H may potentially be complicated by extraneous association phenomena.

The possibility of the importance of tunneling phenomena in these nonenzymic hydride transfer processes was originally raised by Kreevoy and co-workers in their suggestion that an unusual set of secondary isotope effects in the reduction of the 10-methylacridinium cation by several 5,6-dihydrophenanthridines and their 6,6-dideutero derivatives is "quantitatively consistent with the involvement of nuclear tunnelling in the reaction coordinate" (*115*). Subsequently, Formosinho (*120*) used an approximate quantum mechanical treatment based upon an intersecting-state model to treat the data of Kreevoy and Lee (*91*) for the reduction of various quinolinium cations by 10-methyl-9,10-dihydroacridine, and came to the conclusion that tunneling by the hydride nucleus is negligible in solution reactions. More recently, the possibility of large curvature (or corner cutting) tunneling in these processes has been investigated by measuring primary deuterium kinetic isotope effects as a function of the overall equilibrium constants for the hydride transfer reaction (*108*, *116*). In general, it is difficult to distinguish between this process and a variation in primary kinetic isotope effect which arises according to Westheimer–Melander theory (*87*, *97*, *98*) from a variable transition state structure. There is, however, one particular case, namely the reduction of 3-cyanoquinolinium cations by 9-(substituted phenyl)-9,10-dihydroacridines and their 9-deutero derivatives (*116*), in which the experimentally observed variation in k^{H}/k^{D} with K_H is not consistent with a variable transition state structure, and is only readily reconcilable with a corner cutting tunneling process. It should be noted that this latter case also represents by far the most sterically congested set of hydride donor species that have been used in any of these studies.

CONCLUDING REMARKS

The interpretation of these formal hydride transfer reactions in terms of imbalanced development of electronic change within the transition state species leads to a rational merging of the single step hydride transfer mechanism (Scheme 1) and the SET mechanisms of Schemes 2 and 3. As indicated above, reaction coordinate diagrams such as Figs. 9 and 10, as well as the VBCM model, may be usefully used to analyze, at least in a qualitative way, many of the features of the imbalanced transition state within such a merged mechanism.

The likelihood of highly variable structures for the transition state species in these reactions represents a challenge, in terms of devising experiments that will completely define the electronic structures of these species, and an opportunity to test, and refine, many important fundamental concepts of physical organic chemistry. The rich variety of structures and reactivities that are available in nitrogen heterocyclic species makes these systems ideal for the design of experiments which allow the application of multiple criteria to the evaluation of transition state structure. In this author's opinion, the definitive diagnosis of tunneling processes in these reactions will be difficult until such time as the imbalance between electron transfer and hydrogen transfer in these reactions is understood in more detail.

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