Regioselectivity and Kinetics of Hydride Transfer in Substituted 1-Benzyl-3-quinolinecarboxamide Redox Reactions

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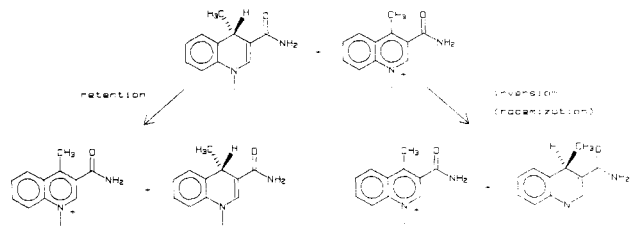
A systematic study on the factors that affect the regioselectivity and rate of hydride transfer in systems involving 1-benzyl-4-methyl-3-quinolinecarboxamides as donors or acceptors is reported. The study reports two major findings: (1) Hydride transfers from borohydride or 1-propyl-1,4-dihydronicotinamide to 1-benzyl-4-methyl-3-quinolinecarboxamide cation display distinct regioselective patterns—borohydride results in hydride transfer to the 2-position of the acceptor and dihydronicotinamide results in hydride transfer to the 4-position of the acceptor. (2) Substitution of the 4-hydrogen by a methyl group on either the oxidant or reductant quinoline lowers the rate constants for hydride transfer by a factor of over 2000. When methyl replaces hydrogen in both the oxidant and reductant, the rate constant for hydride transfer is lowered by a factor of over 5 000 000. These observations are interpreted in terms of a two-step mechanism: (1) formation of a π-complex between the oxidant and reductant stabilized by charge-transfer interactions and (2) rate-determining hydride transfer within the complex.

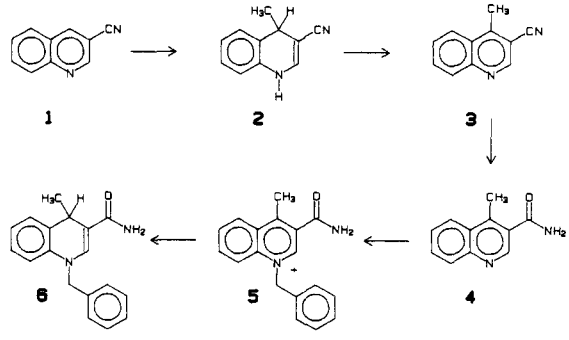
Dihydronicotinamides, synthetic analogues of NADH, have been used extensively to probe the mechanism of hydride transfer in NAD redox reactions.[1] Of particular recent interest are mechanistic studies of hydride transfer reactions involving substituted and elaborated pyridine derivatives.[2] In our laboratory, we have been studying the degenerate transfer of a hydrogen from a reduced 1-alkyldihydronicotinamide to its oxidized conjugate, a process we call transhydrogenation.[3] An important mechanistic question in such reactions is What is the relative orientation of the redox partners in the transhydrogenation transition state? We proposed to address this question by studying transhydrogenation systems involving reduced substrates containing a chiral center at the carbon where transhydrogenation occurs. A typical example is illustrated in Scheme I.

A comparison of the racemization and transhydrogenation rates in such systems offers direct clues to the orientation of the redox partners in the transhydrogenation transition state. Efficient chirality transfer between a chiral 4-methyl-1,4-dihydropyridine and a carbonyl substrate has been reported recently.[4] The success of our proposed experiments, however, hinges on several factors: regioselective hydride transfer from the 4-position of the reduced species to the 4-position of the oxidized species, the absence of competing reactions, and a conveniently measurable reaction rate. In light of these requirements, we carried out and now report a systematic study of the factors affecting the regioselectivity, product distribution, and rate of transhydrogenation in systems involving 1-benzyl-4-methyl-3-quinolinecarboxamides.

Scheme I



Scheme II



Results

Synthesis. The strategy employed to synthesize the oxidized and reduced forms of 1-benzyl-4-methyl-3-quinolinecarboxamides is illustrated in Scheme II. Addition of methylmagnesium bromide to **1** afforded **2**; oxidation of **2** with nitric acid provided **3**. In most cases, **1** could be transformed into **3** in greater than 70% yield without the purification of **2**. The reaction of **3** with alkaline hydrogen peroxide afforded **4** in 60% overall yield based on **1**. Treatment of **4** with neat benzyl bromide and heat produced **5**, which upon reduction with 1-propyl-1,4-dihydronicotinamide produced **6**.

Attempts to obtain **6** by the direct addition of methyl-Grignard to 1-alkyl-3-carbamoylquinolinium gave a mixture of products. For example, the addition of methylmagnesium bromide to 1-benzyl-3-carbamoylquinolinium bromide afforded a 50/50 mixture of the 2- and 4-addition products. This product distribution was not altered even when the reaction temperature was lowered to −77 °C.

Approaches to the Kinetic Studies. The matrix of reductants and oxidants studied and their corresponding kinetic schemes are outlined in Table I. This table incorporates all the kinetically significant pathways necessary to describe the flux of materials over extended time spans including competing reactions, back-reactions, decomposition reactions, and subsequent reactions of products. The

(1) See, for instance: Klinman, J. P. *CRC Crit. Rev. Biochem.* **1981**, *10*, 39. Powell, M. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 7139.
(2) Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 257. Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *J. Org. Chem.* **1983**, *48*, 2053. Bunting, J. W.; Chew, V. S. F.; Chu, G.; Fitzgerald, N. P.; Gunasekara, A.; Oh, H. T. P. *Bioorg. Chem.* **1984**, *12*, 141. Bunting, J. W.; Fitzgerald, N. P. *Can. J. Chem.* **1985**, *63*, 655. Bunting J. W.; Brewer, *J. C. Can. J. Chem.* **1985**, *63*, 1245.
(3) Van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 8056. Van Eikeren, P.; Kenney, P.; Tokamakian, R. *J. Am. Chem. Soc.* **1979**, *101*, 7402.
(4) Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989.

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Table I. Matrix of Hydride Transfer Studies and Their Corresponding Kinetic Schemes[a]

OXIDANT / REDUCTANT	QS	MQS
14DHN	14DHN + QS $\xrightarrow{k_1}$ NS + 14DHQ 14DHN + QS $\xrightarrow{k_2}$ NS + 12DHQ 12DHQ + QS $\xrightarrow{k_3}$ QS + 14DHQ	14DHN + MQS $\xrightarrow{k_9}$ NS + M14DHQ 14DHN + MQS $\underset{k_{11}}{\overset{k_{10}}{\rightleftharpoons}}$ NS + M12DHQ M12DHQ+MQS $\xrightarrow{k_8}$ MQS+M14DHQ
14DHQ	14DHQ + QS* $\underset{k_4}{\overset{k_4}{\rightleftharpoons}}$ QS + 14DHQ* 14DHQ $\xrightarrow{k_{ox}}$ QS	14DHQ + MQS $\xrightarrow{k_7}$ QS + M14DHQ
12DHQ	12DHQ + QS $\xrightarrow{k_3}$ QS + 14DHQ 14DHQ $\xrightarrow{k_{ox}}$ QS	12DHQ + MQS $\xrightarrow{k_{12}}$ QS + M14DHQ 14DHQ + MQS $\xrightarrow{k_7}$ QS + M14DHQ 12DHQ + QS $\xrightarrow{k_3}$ QS + 14DHQ 14DHQ $\xrightarrow{k_{ox}}$ QS
M12DHQ	M12DHQ + QS $\xrightarrow{k_5}$ MQS + 14DHQ M12DHQ+MQS $\xrightarrow{k_8}$ MQS+M14DHQ 14DHQ + MQS $\xrightarrow{k_7}$ QS + M14DHQ 14DHQ $\xrightarrow{k_{ox}}$ QS	M12DHQ+MQS $\xrightarrow{k_8}$ MQS+M14DHQ
M14DHQ	M14DHQ + QS $\underset{k_7}{\overset{k_8}{\rightleftharpoons}}$ MQS + 14DHQ M12DHQ + QS $\xrightarrow{k_5}$ MQS + 14DHQ 14DHQ $\xrightarrow{k_{ox}}$ QS	M14DHQ+MQS* $\underset{k_{13}}{\overset{k_{13}}{\rightleftharpoons}}$ MQS+M14DHQ*

[a] NS corresponds to 1-benzylnicotinamide cation.

bases for choosing the kinetic schemes shown in Table I are described below.

The kinetic schemes in Table I contain an aggregate of 14 unique rate constants. Their values were obtained from computer fits of the experimental concentration vs. time data. The simulations were carried out in the sequence specified in Table II in order to arrive at an internally consistent set of rate constants. A given simulation used previously determined rate constants (fixed parameters) and varied one unknown rate constant (variable parameter) until best visual fit to the data was obtained. Estimates of the experimental error in the rate constant were obtained by analyzing the sensitivity of the visual fit to increases or decreases in the value of the variable parameter. In two simulations, a fit to the data was obtained by using more than one variable parameter. However, sensitivity studies on these variable parameters clearly indicated that the information content in our concentration vs. time data was sufficient to obtain unique and thus accurate values for the rate constants.

Results of Hydride Transfer Studies. The measured rate constants for the hydride transfer experiments described in Tables I and II are summarized in Table III. All measurements except for one were carried out in methanol solvent at 22 ± 1 °C. The experimental protocol and the results are described in greater detail in the following sections.

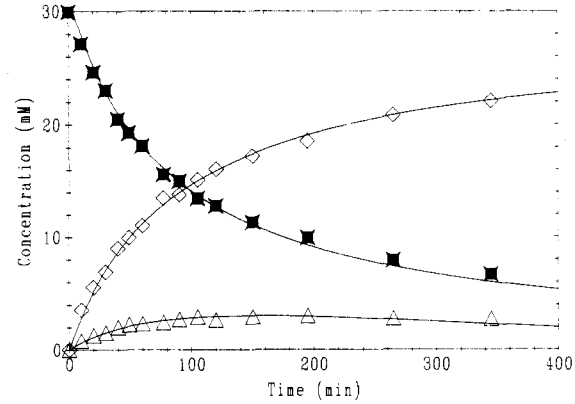

Figure 1. Concentration of 14DHN (■), M14DHQ (◇), and M12DHQ (△) vs. time in experiment number 7. Initial conditions: 14DHN, 31.5 mM; MQS, 31.5 mM; in methanol at 22 °C. Calculated lines based on kinetic scheme given in Table I using above initial conditions and the rate constants reported in Table III.

(a) Experiment 1. Despite our best efforts to maintain anaerobic conditions, 14DHQ undergoes a slow first-order oxidation to QS. By contrast, M14DHQ is not labile under the same reaction conditions.

(b) Experiment 2. The progress of this reaction was monitored using ^{14}C-labeled QS and observing the rise in specific activity of 14DHQ as a function of time. The experiment was performed and analyzed as reported previously.[5] Rate constants for this reaction (nine total) were measured over a 40 °C range. On the basis of this information we calculate values of 50.1 kJ/mol-K and −170 J/mol for $\Delta H°^{\ddagger}$ and $\Delta S°^{\ddagger}$, respectively. An HPLC analysis of the reaction mixture after 24 h of transhydrogenation (approximately 10 half-lives) failed to detect the presence of 12DHQ. This suggests that its formation is exceedingly slow and/or highly unfavorable. On the basis of our detection limits of 12DHQ, we estimate the equilibrium constant for 12DHQ to 14DHQ isomerization to be greater than 99.5/0.5 = 200.

(c) Experiment 4. Since 12DHQ is unstable with respect to 14DHQ, only the forward reaction is kinetically significant.

(d) Experiment 5. By restricting the analysis to the early stages of the reaction (less than 10% conversion), contributions due to the reverse reaction via the microscopic reverse of k_7 can be neglected.

(e) Experiment 6. Hydride transfer from 14DHN can occur by two routes: the major route to the 4-position of QS and the minor route to the 2-position of QS. However, since we are unable to measure the minor route in the absence of the major route, we had to vary two kinetic parameters to obtain a best fit simulation. Note that the decomposition of 14DHQ can be neglected because the overall reaction is quite rapid.

(f) Experiment 7. As described in experiment 6, we are unable to measure the minor hydride transfer route in the absence of the major route. In addition, the position of equilibrium for the second reaction is not sufficiently far to the right to allow us to ignore the back reaction. Consequently, we had to fit three parameters in our simulation. Despite these complexities, we are confident that the rate constants reported in Table III are accurate. A typical result is shown in Figure 1. A sensitivity study of the variable parameters values indicated that the best fit to the three parameters was unique, that is, we were unable to find significantly different but chemically rea-

(5) Van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 8056.

Table II. Approaches to the Measurement of Kinetic Constants

	experiment				simulation		results
expt	reductant	oxidant	HPLC condtns	analytical method	fixed parameter	variable parameter	figure number
1	14DHQ		B	1	none	k_{ox}	
2	14DHQ	QS*	C	3	none	k_4	
3	M12DHQ	MQS	A	1	none	k_6	
4	12DHQ	QS		2	k_{ox}	k_3	
5	14DHQ	MQS	B	1	k_{ox}	k_7	
6	14DHN	QS	A	1	k_3	k_1, k_2	
7	14DHN	MQS	A	1	k_6	k_9, k_{10}, k_{11}	1
8	M12DHQ	QS	B	1	k_{ox}, k_6, k_7	k_5	
9	12DHQ	MQS	B	1	k_{ox}, k_3, k_7	k_{12}	2
10	M14DHQ	QS	B	1	k_{ox}, k_5, k_7	k_8	
11	M14DHQ	MQS	C	3	none	k_{13}	

Table III. Measured Rate Constants for the Transhydrogenations Described in Tables I and II

rate constant	value (M^{-1} min^{-1})	$\Delta G^{0\ddagger}$ (kcal/mol)	comment
k_{ox}	1.0×10^{-4}	25.1	*a*, *d*
k_1	1.1×10^{2}	16.9	*c*
k_2	2.86	19.1	*d*
k_3	1.40×10^{1}	18.1	*c*
k_4	1.1	20.0	*c*
k_5	4.1×10^{1}	17.5	*c*
k_6	1.35×10^{-1}	20.9	*c*
k_7	4.5×10^{-4}	24.0	*d*
k_8	5×10^{-4}	24.2	*d*
k_9	3.20×10^{-1}	20.4	*d*
k_{10}	7.2×10^{-2}	21.2	*d*
k_{11}	2.6×10^{-3}	23.0	*d*
k_{12}	4.55×10^{-1}	20.2	*d*
k_{13}	2×10^{-7}	29.2	*b*

[a] First-order rate constant, min^{-1}. [b] Estimated as described in text. [c] Experimental error estimated as less than ±5%. [d] Experimental error estimated as ±15%.

sonable combinations of rate constants that gave a better fit.

(g) Experiment 9. Since samples of 12DHQ are contaminated with significant quantities of 14DHQ, the analysis of this experiment requires special comment. A typical run is shown in Figure 2. Initial attempts to fit k_{12} to the experimental concentration vs. time profile failed to provide an acceptable fit. An examination of the reaction profile reveals that the reaction displays an induction period typical of autocatalytic processes. The origin of the induction period becomes apparent from an examination of the kinetic scheme for the reaction shown in Table I. Samples of 12DHQ disappear by two routes: hydride transfer to MQS to form M14DHQ and isomerization via hydride transfer to QS to form 14DHQ. The relative rates of 12DHQ disappearance via these two routes depend on two factors: the concentrations of MQS vs. QS and the values of the rate constants k_{12} and k_3. Given that the initial concentration of QS is expected to be zero (or at least very low), one would expect 12DHQ disappearance via the isomerization route to be insignificant in the initial stages of the reaction despite the larger value of k_3 over k_{12}. However, since hydride transfer to MQS produces QS, over time the contribution by the isomerization route increases. Furthermore, in the isomerization route the concentration of QS remains constant. Hence, the process is autocatalytic and an induction period is expected. However, what we did not appreciate is the low level of QS needed for catalysis. When we set the initial concentration of QS to zero in our simulation, we obtained the rate profile shown in Figure 2b. By contrast, setting the initial concentration of QS to 2% of the sum of initial 12DHQ and 14DHQ concentrations dramatically shortens the induction period and provides an excellent fit to the

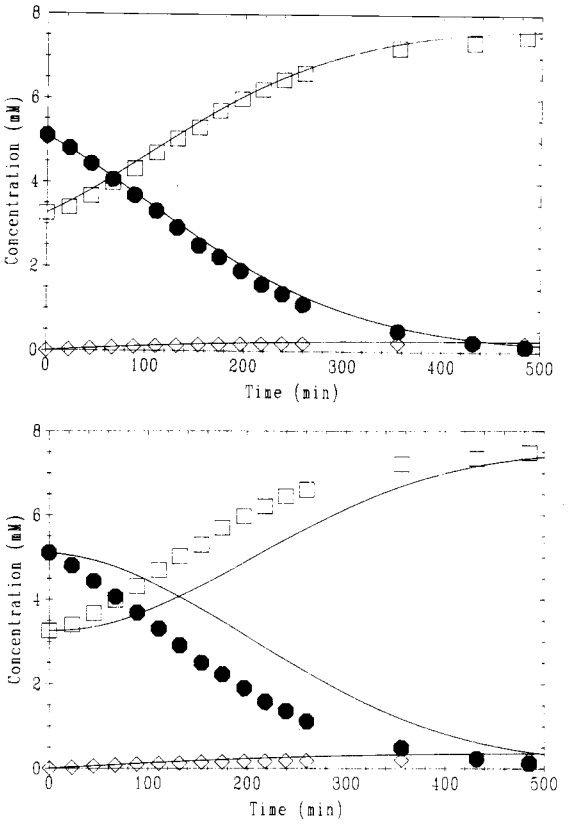

Figure 2. (a) Concentration of 12DHQ (●), 14DHQ (□), and M14DHQ (◇) vs. time in experiment 9. Initial conditions: 12DHQ, 5.10 mM; 14DHQ, 3.26 mM; MQS, 6.20 mM; in methanol at 23 °C. Calculated lines based on kinetic scheme given in Table I using above initial conditions, an initial concentration of QS of 0.16 mM, and the rate constants reported in Table III. (b) Same as (a) except that the calculated line sets the initial concentration of QS = 0.

experimentally observed concentration vs. time profile (Figure 2a). Presumably, the 2% oxidized QS impurity arises from air-oxidation of 12DHQ and 14DHQ during preparation, purification, and storage.

(h) Experiment 11. Determining the value of k_{13} proved technically difficult because the rate of the reaction is extremely slow. When MQS labeled with deuterium in the benzyl group was combined with M14DHQ and the reaction mixture examined by NMR over a 24-h period, we were unable to detect the production of unlabeled MQS. Control experiments indicated that we could detect the production of 2% unlabeled MQS. Thus we conclude that the transhydrogenation rate is exceeding slow. The value of k_{13} was estimated to be $\approx 2 \times 10^{-7}$ M^{-1} min^{-1} on the basis that the substitution of methyl for hydrogen at the 4-position alters the rate constant of hydride transfer

Table IV. Regioselectivity during Dihydronicotinamide and Sodium Borohydride Reductions

oxidant	C-4/C-2 selectivity	
	1-Pr-DHN	borohydride
NS	60/1	*a*
QS	38/1	1/4.3
1-methyl-3-bromoquinolinium[b]	6/1	1/20
MQS	4.4/1	1/166

[a] Hydride transfer occurs predominantly to the 6-position. Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *J. Org. Chem.* **1983**, *48*, 2053. [b] Bunting, J. W.; Fitzgerald, N. P. *Can. J. Chem.* **1985**, *63*, 655.

by factors of 4.1×10^{-4} and 4.5×10^{-4} in the oxidant and reductant, respectively.

Regioselectivity in Dihydropyridine and Dihydroquinoline Reductions. Reductions of NS, QS, and MQS by 14DHN display a strong preference for hydride transfer to the 4-position. The regioselectivity ratios, the ratio of transfer to the 4-position vs. the 2-position in the oxidant, for several experiments are given in Table IV. The regioselectivity ratios are based on the rate constants reported in Table III. By contrast, reductions of the same oxidants by $NaBH_4$ display a striking preference for hydride transfer to the 2-position. For example, the inverse addition of the oxidant to a methanolic solution containing excess sodium borohydride followed by immediate HPLC analysis gave the product ratios shown in Table IV.

Discussion

Effects of Structure on Hydride Transfer Rates. 1,4-Dihydroquinolines are weaker reducing agents than 1,4-dihydronicotinamides, but transhydrogenation rates are more rapid for the former. For example, hydride transfer from 1-benzyl-1,4-dihydronicotinamide to 1-benzyl-3-carbamoylquinolinium is practically quantitative. However, the degenerate transhydrogenation reaction involving 1,4-dihydroquinolines is more rapid than the corresponding reaction for 1,4-dihydropyridines. For example, the measured second-order rate constant for 1-benzyl-1,4-dihydro-3-carbamoylquinoline/1-benzyl-3-carbamoylquinolinium transhydrogenation is 2.4 M^{-1} min^{-1} at 40 °C. By contrast, the measured second-order rate constant for the corresponding nicotinamide reaction is 0.199 M^{-1} at the same temperature. This represents a 12-fold difference in rates.

The replacement of the 4-hydrogen by a methyl group on either the oxidant or reductant quinoline dramatically lowers the rate of hydride transfer. For example, substitution of methyl for one 4-hydrogen on 1,4-dihydroquinoline (M14DHQ vs. 14DHQ) lowers the rate constant for hydride donation reaction by a factor of 2200. Similarly, substitution of methyl for the 4-hydrogen on quinolinium cation (MQS vs. QS) lowers the rate constant for hydride acceptance by a factor of 2400. When 4-methyl substitution occurs on both the reductant and the oxidant, we estimate that the rate constant for hydride transfer is reduced by a factor of 5 000 000.

Regioselectivity of Hydride Transfer Reaction. Hydride transfer from borohydride or dihydronicotinamide shows distinct regioselective patterns—borohydride results in hydride transfer to the 2-position and dihydronicotinamide results in hydride transfer to the 4-position. This observation has been previously reported by Kreevoy and co-workers.[6] The experimentally observed patterns are summarized in Table IV.

(6) Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *J. Org. Chem.* **1983**, *48*, 2053.

Table V. Second-Order Rate Constants for Degenerate Transhydrogenation

reduced member of redox pair	k_2 (M^{-1} min^{-1})	temp (°C)	ref	solvent
1-methyl-1,4-dihydroacridine	2.58	25	*b*	*e*
14DHQ	1.1	23	*a*	*d*
1-methyl-1,4-dihydrophenanthridine	1.08	25	*b*	*e*
1-benzyl-3-carbonitrile-1,4-dihydroquinoline	0.078	25	*b*	*e*
1-benzyl-1,4-dihydronicotinamide	0.033	40	*c*	*f*
M14DHQ	2×10^{-7}	23	*a*	*d*

[a] This study. [b] Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 257. [c] van Eikeren, P.; Grier, D. L. *J. Am. Chem. Soc.* **1977**, *99*, 8057. [d] Methanol. [e] 2-Propanol/water (4/1). [f] Acetonitrile/aqueous buffer (1/3).

Hydride transfer regioselectivity from dihydropyridines or dihydroquinolines is maintained even when attack at the 4-position of the oxidant is sterically hindered. For example, substitution of methyl for the 4-hydrogen in QS only reduces the selectivity of hydride transfer to C-4 from 97.4% to 80.4%. This is striking given that the substitution reduces the second-order rate constant, and hence the rate of hydride transfer to C-4, from 110 M^{-1} min^{-1} to 0.32 M^{-1} min^{-1}, a factor of 340.

Mechanism To Account for Regioselectivity and Structural Effects. A mechanism consistent with the above observations is outlined below:

$$A^+ + HB \rightleftarrows A^+ \cdot HB \text{ (fast)}$$

$$A^+ \cdot HB \rightarrow AH \cdot B^+ \text{ (slow)}$$

$$AH \cdot B^+ \rightleftarrows AH + B^+ \text{ (fast)}$$

This mechanism is similar to ones proposed by Bunting and Sindhuatmadja[7] and Kreevoy and co-workers.[8] In this mechanism, oxidant and reductant combine rapidly, forming a noncovalent complex. Hydride transfer occurs within the complex and is rate-determining, consistent with reported primary isotope effects. The regioselectivity is principally dictated by the orientation of the redox partners in the complex; the rate constant for hydride transfer is principally dictated by the stability of the complex.

The complex formed with borohydride has several distinguishing features. Complex formation between the negatively charged borohydride or borohydride derivatives and the positively charged nitrogen is driven by coulombic attraction. The resulting orientation explains the prominence of hydride transfer to the 2-position in quinolines and 6-position in nicotinamides.

The complex formed between a neutral 1,4-dihydropyridine and a quinolinium cation is stabilized by a charge-transfer interaction in which the π-system of the reductant donates electron density into the π-system of the oxidant. Charge-transfer interactions for NAD analogues have been reported by several authors.[9] This model is consistent with the trend in rate constant values for degenerate transhydrogenation reactions, all of which have equilibrium constants equal to 1. Some typical values are given in Table V. The data suggest that the stability of the charge-transfer complex is affected by two factors: (1) the size of the π-system and (2) the distance that the π-systems can approach each other. Given that the strength of the charge-transfer interaction drops off rapidly

(7) Bunting, J. W.; Sindhuatmadja, S. *J. Org. Chem.* **1981**, *104*, 4211.
(8) Roberts, R. M.; Ostovic, D.; Kreevoy, M. M. *Faraday Discuss. Chem. Soc.* **1982**, *74*, 257.
(9) Bruice, T. C.; Main, L.; Smith, S.; Bruice, P. Y. *J. Am. Chem. Soc.* **1971**, *93*, 7327. Blankenhorn, G. *Eur. J. Biochem.* **1976**, *67*, 67.

with distance, substitution of a bulky methyl group for a 4-hydrogen is expected to inhibit the interaction of π-systems and thus have large effects on the hydride transfer rate constants. It is important to note that the above analysis could only come from an examination of the degenerate transhydrogenation reaction. An analogous analysis for nondegenerate reactions is complicated by the fact that the rate constants are strongly influenced by the equilibrium constant of the reaction in which they participate.[10]

The observation that the rate constant for hydride transfer decreases when one of the 4-hydrogens in the dihydroquinoline (rather than the oxidized species) is replaced by a methyl group deserves special comment. In the π-complex, this methyl group would be located on the side of the plane opposite to the oxidized partner. Consequently, such methyl substitution would be expected to have a minimal effect on the stability of the π-complex. The effect on the rate constant, then, must reflect the additional free energy required to reach the transhydrogenation transition state. Presumably, more free energy is required to change the hydridization at C-4 from sp^3 to sp^2 when the more massive methyl group is attached at C-4.

Experimental Section

Analytical separations were carried out on a Hewlett-Packard 1090A liquid chromatograph, equipped with a Hewlett-Packard 1040A diode array UV/vis detector, or on a Varian 5000 liquid chromatograph, equipped with a Varian "VariChrom" UV/vis detector. Peak areas were recorded on a Spectra-Physics SP4270 integrator. Proton NMR spectra were recorded on IBM NR/200 FT or Varian EM-360L spectrometers. (J values are in hertz). IR spectra were recorded on Perkin-Elmer 980 or 1330 spectrometers. UV/vis spectra were recorded as part of the HPLC characterization using the HP 1040A detector or on a Beckman DU-7 spectrometer. Radioactivity measurements were performed on a Beckman LS 9000 liquid scintillation counter. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Solvents for preparative work were reagent grade. All kinetic experiments were carried out at 22 ± 1 °C in absolute methanol solvent except for experiment 5 which included 20% (v/v) tetrahydrofuran (THF) to improve solubility. Methanol for kinetic experiments was HPLC grade, and THF was reagent grade. All chromatographic elution solvents were HPLC grade.

HPLC Separation Conditions. Three HPLC methods were employed:

HPLC Condition A. A Hewlett-Packard Hypersil ODS 100 × 2.1 mm column was employed, with a flow rate of 0.4 mL/min. The eluting solvent as 67/33 (v/v) water/acetonitrile, and detection was at 245 nm.

HPLC Condition B. The condition A column and flow rate were used, and the eluting solvent was 50/50 (v/v) methanol/0.1 M aqueous potassium phosphate buffer, 0.02 M triethylamine, pH 7.3. Detection of quinolinium salts and 1,2-dihydroquinolines was at 245 nm, and detection of 1,4-dihydroquinolines was at 345 nm.

HPLC Condition C. A Waters μBondapak ODS 250 × 4.6 mm column was employed, with a flow rate of 1.0 mL/min. The eluting solvent was 68/32 (v/v) acetonitrile/1% aqueous ammonium bicarbonate. Detection was at 335 nm.

Kinetic Methods. Solutions of the appropriate concentration of each reactant were prepared in volumetric flasks. In a typical experiment, 2.00 mL of a 3.00 mM solution of the oxidized reagent was combined with 2.00 mL of a 3.00 mM solution of the reduced reagent and the mixture maintained under nitrogen. In some experiments, biphenyl was added to the reaction mixture as an internal standard at a concentration of ca. 1 mM. Analytical methods appropriate to each experiment were employed.

Analytical Method 1. Aliquots were removed at appropriate time intervals, diluted with methanol, and injected into the liquid chromatograph. The peak areas obtained for each reaction component were converted to concentration by using previously determined response factors. If the time interval for removal of aliquots was smaller than the analysis time, the aliquots removed were immediately cooled to −78 °C in a dry ice/CH_2Cl_2 bath in order to quench the reaction. The cooled aliquots were later individually warmed slightly and immediately analyzed while still at a temperature well below 0 °C.

Analytical Method 2. This method is identical with analytical method 1, except that the aliquots were analyzed by measuring the absorbance at 409 nm in a spectrophotometer. The absorbance was converted to concentration by using the appropriate extinction coefficient.

Analytical Method 3. This method was employed to measure the disappearance of radioactivity in the reactant and the appearance of radioactivity in the conjugate species as a function of time. In a typical experiment, reaction aliquots (100 μL) were removed and injected into the HPLC, and the components were separated according to HPLC condition C. The effluent corresponding to each separated peak was collected into a scintillation vial. An equal volume of Bray's solution was added and the radioactivity determined by liquid scintillation counting. Observed counts were corrected for quenching and converted to disintegrations per minute (dpm). These, in turn, were converted to concentrations on the basis of the known specific activity of the reactants.

Determinations of Rate Constants. The rate constants reported in Table II were obtained from computer fits to the experimental concentration vs. time data. The set of differential equations describing the kinetic schemes outlined in Table I were solved by numerical integration using the solving package, ODEPACK,[11] on a Digital Equipment Corporation VAX 8600. ODEPACK solves both stiff and nonstiff systems of initial value problems consisting of coupled, first-order ordinary differential equations in normal form by using a variable-step Adams-Bashforth method in double precision.[12] In most cases, a single rate constant was varied until the best visual fit between the calculated and the experimental concentration vs. time data was obtained. Estimates of the experimental error in the rate constant (Table III) were obtained by analyzing the sensitivity of the visual fit to alterations in the reported value. Specifically, we estimated the amount that the reported rate constant needed to be lowered or raised in order to obtain a calculated concentration vs. time profile that clearly did not fit the experimental data.

Syntheses. 4-Methyl-1,4-dihydro-3-quinolinecarbonitrile (2). The title compound was prepared by an adaptation of the procedure of Matsumori.[13] Methylmagnesium bromide (Aldrich: 15.3 g, 130 mmol in 45 mL of ether) was added dropwise with stirring to a solution of 3-quinolinecarbonitrile (Aldrich: 10 g, 65 mmol) in anhydrous tetrahydrofuran (80 mL) maintained at 0 °C. The mixture was stirred at 0 °C for 4 h and then left to stir overnight at room temperature. The solvent was removed under vacuum, and the tarry brown residue was dissolved in a solution of ammonium chloride (20 g in 100 mL of water). The aqueous solution was extracted with dichloromethane. The organic layers were combined washed with water, and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to produce a brown solid. This product could be successfully oxidized without further purification. Recrystallization from ethanol/water yielded 7.26 g (66%), orange-brown crystals, mp 87–88 °C (lit.[14] mp 89–90 °C). IR (KBr): 3280, 2175, 1480, 1290, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3–1.5 (d, J = 7, 3 H), 3.6–3.9, (q, J = 7, 1 H), 6.5–7.3 (m, 6 H).

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4-Methyl-3-quinolinecarbonitrile (3). The title compound was prepared by a modification of the procedure of Ferles and co-workers.[15] 4-Methyl-1,4-dihydro-3-quinolinecarbonitrile (2.0 g, 12 mmol) was mixed with a 1:3 (v/v) concentrated nitric acid/water solution (67 mL) and heated to 70 °C with stirring for 1.5 h. The reaction was judged complete when the solution became homogeneous (one phase). The mixture was cooled, and the product was precipitated by the addition of concentrated ammonium hydroxide. The green product was recrystallized from methanol, yielding 1.43 g (72%) of light brown crystals, mp 139–141 °C (lit.[16] 140–141 °C). UV (CH_3CN): 215, 235 max, 315 (nm). IR (KBr): 3420, 2220, 1380, 755 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.0 (s, 1 H), 7.6–8.3 (m, 4 H), 9.0 (s, 1 H).

4-Methyl-3-quinolinecarboxamide (4). The title compound was prepared by an adaptation of the procedure of Noller.[17] 4-Methyl-3-quinolinecarbonitrile (4.03 g, 24 mmol) was dissolved in a mixture of 95% ethanol (15 mL) and hydrogen peroxide (Aldrich, 30%; 10 mL). Aqueous sodium hydroxide (6 M, 1 mL) was added; the yellow solution warmed up and evolved oxygen. The temperature of the solution was kept under 55 °C by periodic cooling in an ice bath. After the solution stopped evolving heat, it was maintained at 50 °C for 2.5 h. The solution was concentration on a rotary evaporator and then stored in a refrigerator overnight (20 °C). The precipitate that formed was collected by filtration to yield 3.80 g (85%), white crystals, mp 196–197 °C. The melting point was unchanged upon recrystallization from ethanol/water. The compound had a pK_a of 3.1 ± 0.2 on the basis of the titration curve obtained by titrating a sample of the compound against 0.1 M HCl. UV (HPLC condition B): 230 max, 284 (nm). IR (KBr): 3291, 3166, 1701, 744 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.75 (s, 3 H), 7.65–7.72 (t, J = 7, 1 H), 7.78–7.85 (m, 2 H), 8.02–8.09 (m, 2 H), 8.18–8.22 (d, J = 7, 1 H), 8.61 (s, 1 H). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41, N, 15.05. Found: C, 71.08; H, 5.45; N, 15.04.

1-Benzyl-4-methyl-3-carbamoylquinolinium Bromide (5). The title compound was prepared by an adaptation of the procedure of Roberts et al.[18] Solid 4-methyl-3-quinolinecarboxamide (1.00 g, 5.37 mmol) was placed into a 100-mL round-bottom flask and heated in an oil bath to 130 °C. Sufficient benzyl bromide (Aldrich: 0.80 mL, 6.73 mmol) was added dropwise to the flask to cover the solid. Brown crystals appeared after several minutes; the mixture was allowed to cool to room temperature after 20 min. The crystalline mass was ground with a mortar and pestle and washed repeatedly with ether to remove excess benzyl bromide and most of the colored impurities. Recrystallization from methanol/ether offered 1.50 g (78%) of white needles, mp 207–208 °C dec. NMR and elemental analysis revealed that the needles contained 34 mol % methanol of crystallization. Isotopically labeled forms of this compound were also synthesized, using benzyl-d_7 bromide and benzyl-^{14}C bromide. UV (HPLC condition B): 240 max, 322 (nm). IR (KBr): 3300, 3144, 1678, 1391 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.75 (s, 3 H), 6.38 (s, 2 H), 7.39 (s, 5 H), 7.65–7.72 (t, J = 7, 1 H), 7.78–7.85 (m, 2 H), 8.02–8.09 (m, 2 H), 8.18–8.22 (d, J = 7, 1 H), 8.61 (s, 1 H). Anal. Calcd for $C_{18}H_{17}BrN_2O \cdot 0.34CH_3OH$: C, 59.83; H, 5.03; N, 7.61. Found: C, 59.83; H, 4.90; N, 7.71.

1-Benzyl-3-carbamoyl-1,4-dihydro-4-methylquinoline (6). The title compound was prepared by an adaptation of the procedure of Shinkai et al.[19] 1-Benzyl-4-methyl-3-carbamoylquinolinium bromide (570 mg, 1.6 mmol) was dissolved in methanol (15 mL). A solution of 1-propyl-1,4-dihydronicotinamide (330 mg, 2.0 mmol) in methanol (5 mL) was added dropwise with stirring under nitrogen. The stirred solution was heated to 40 °C for 3 h. The solvent was removed under vacuum and the orange-yellow residue taken up in 25 mL of chloroform. The chloroform solution was washed with two 3-mL portions of water and dried over anhydrous sodium sulfate. The chloroform was removed under vacuum to give a yellow glass. ^1H NMR analysis of this glass confirmed its structure and revealed that it was contaminated by 8–12% of the 1,2-isomer. The glass darkened rapidly upon exposure to air. We were unable to crystallize the substance. UV (HPLC condition B): 239 sh, 334 max (nm). IR (KBr): 3336, 3204, 1650, 1382, 751 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30–1.33 (d, J = 7, 3 H), 3.85–3.94 (q, J = 7, 1 H), 4.83–4.86 (d, J = 7, 2 H), 5.61 (s, 2 H), 6.67–6.71 (dd, J_1 = 7, J_2 = 2, 1 H), 6.92–7.07 (qd with s [6.99], J_1 = 7, J_2 = 2, 2 H), 7.12–7.16 (dd, J_1 = 7, J_2 = 2, 1 H), 7.19–7.36 (m, 5 H), 7.42 (s, 1 H).

1-Benzyl-3-carbamoyl-1,2-dihydro-4-methylquinoline. The title compound was prepared by an adaptation of the procedure of Roberts et al.[20] 1-Benzyl-4-methyl-3-carbamoylquinolinium bromide (500 mg, 1.4 mmol) was dissolved in a 3:2 (v/v) mixture of methanol/water (15 mL). The solution was cooled to 0 °C in an ice bath and stirred under nitrogen. Sodium borohydride (Aldrich: 53 mg, 1.4 mmol) in water (5 mL) was added dropwise to the solution, causing the immediate formation of yellow crystals. The mixture was stirred for 1 h; the crystals were collected by filtration and dried under vacuum, yielding 345 mg (89%) of yellow crystals that sublimed at 130 °C. This compound was also prepared with deuterium at the 2-position by reduction with sodium borodeuteride. The deuteriated compound has an identical NMR spectrum except that the peak at δ 4.15 had an area corresponding to only one hydrogen. UV (condition B) 242 max, 285 sh, 370 (nm) IR (KBr) 3368, 3177, 1647, 1598, 640 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.25 (t, J = 1.5, 3 H), 4.15 (d, J = 1.5, 2 H), 4.42 (s, 2 H), 5.71–6.17 (br s, 2 H), 6.55–6.59 (dd, J_1 = 7, J_2 = 1, 1 H), 6.64–6.72 (td, J_1, = 7, J_2 = 1, 1 H), 7.03–7.12 (td, J_1 = 7, J_2 = 2, 1 H), 7.23–7.28 (dd, J_1 = 7, J_2 = 2, 1 H), 7.30–7.33 (m, 5 H). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.54; N, 10.07. Found: C, 77.77; H, 6.55; N, 10.04.

1-Benzyl-1,4-dihydronicotinamide and 1-propyl-1,4-dihydronicotinamide were prepared according to the procedure of Anderson and Berkelhammer.[21]

1-Benzyl-3-carbamoylquinolinium bromide was prepared from 3-quinolinecarboxamide by the same procedure used to make its 4-methyl analogue above. Characterization of the product was consistent with that reported by Shinkai et al.[22] An isotopically labeled compound was prepared by using benzyl-^{14}C bromide.

1-Benzyl-1,4-dihydro-3-quinolinecarboxamide was prepared according to the procedure of Shinkai et al.[22]

1-Benzyl-1,2-dihydro-3-quinolinecarboxamide was prepared by the same procedure used to make its 4-methyl analogue above, except that inverse addition of the quinolinium salt precursor to a 40-fold excess of sodium borohydride was utilized, and the mixture was allowed to react for only 15 min at room temperature. The recrystallized product contained 24% of the 1,4-isomer. Addition of sodium borohydride to the quinolinium salt and/or a longer reaction time results in substantially greater amounts of the 1,4-isomer. Characterization of the product was consistent with that reported by Roberts and co-workers.[23]

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Registry No. 1, 34846-64-5; 2, 73013-64-6; 3, 73013-65-7; 4, 109391-70-0; 5·Br, 109391-71-1; 6, 109391-72-2; QS·Br, 70293-11-7; 14DHN, 952-92-1; 14DHQ, 17260-79-6; 12DHQ, 85749-96-8; M12DHQ, 109391-73-3; 1-propyl-1,14-dihydronicotinamide, 17750-24-2.

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