Hydride Transfer and Oxyanion Addition Equilibria of NAD^+ Analogues[1a]

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Equilibrium constants, K, have been determined for the reduction of 10-methylacridinium ion by 15 N-heterocyclic hydride donors: acridine, quinoline, pyridine, and phenanthridine derivatives. The solvent was a mixture of 2-propanol and water in the ratio 4:1 by volume. Reduction potentials have been estimated for the corresponding cations in aqueous solution by assuming that the K's would be the same and accepting −361 mV as the reduction potential of the 3-(aminocarbonyl)-1-benzylpyridinium ion. These reduction potentials span 430 mV. Values of pK_R have also been determined for six of the cations in the same solvent. For derivatives of the same ring system, $-\Delta \log K$ is approximately equal to ΔpK_R, but a 4 log unit discrepancy appears when phenanthridine derivatives are compared with the 9-methylacridinium ion.

Correlation of rate constants with equilibrium constants has, historically, been one of the most fruitful sources of insight into reaction mechanism and transition-state structure.[2-4] However, apart from acid dissociation constants and one-electron redox reactions, relatively few equilibrium constants have been available.[5] Particularly, there have been few sets of equilibrium constants for analogous reactions, measured under similar conditions.

In the present paper we present 15 equilibrium constants, K, for reactions of the type shown in eq 1, where

$$Ac^+ + HA_i \rightleftharpoons HAc + A_i^+ \qquad (1)$$

Ac^+ is the 10-methylacridinium ion, **1a**, and the A_i^+ are a variety of substituted pyridinium, quinolinium, acridinium, and phenanthridinium ions, **2**–**4**. These ions are analogues of the enzyme cofactor, nicotinamide adenine dinucleotide (NAD^+).

The reductants, HAc and HA_i, are the 9,10-, 1,4-, or 1,2-dihydro derivatives, **1H**–**4H**. To determine equilibrium constants too large for direct measurement, 3,10-dimethyl-5-deazaisoalloxazine, **5**, was used as a secondary standard. (See Chart I.) Equilibrium constants for the reduction of three phenanthridinium ions, **4a**–**c**, by the conjugate base of **5**, **5H**, were measured. Since K values for **4a**–**c** could be directly determined, by reaction of **4Ha**–**c** with **1a**, the equilibrium constant for the reaction of **5H** with **1a** could be calculated. With two exceptions, other K values, for reactions with **1a**, either were measured directly or were calculated from measured equilibrium constants for reaction with **5**. In the exceptional cases, one of the phenanthridinium ions or quinolinium ions was used as the secondary reference.

The equilibrium constants have all been measured at 25 °C, in a solvent consisting of four parts of isopropyl alcohol to one part of water by volume. This solvent system was chosen because it dissolves all the participants in these equilibria and because its isopropyl alcohol component is an efficient trapper of free radicals.[6] We believe that this last property frees our system of byproducts formed in free-radical chain reactions. The K values span a total range of about 10^{12}. Since the two-electron reduction potential vs. the standard hydrogen electrode is known for **3d** in water as solvent, these equilibrium constants give an approximation of the standard reduction potentials of the cations in water. To make this calculation we have assumed that equilibrium constants for reactions of neutrals with cations are the same in water as in our mixed solvent. This seems reasonable, since the overall charge type is unchanged by the reaction and the structure of products and reactants is similar. These reduction potentials span ~430 mV. The results and methodology presented here will make it easy to add more equilibrium constants of simliar type in the future. Values of K were determined by measuring rate constants for forward and reverse reactions, k_+ and k_-, spectrophotometrically; k_+/k_- was equated to K. The reactants were chosen so that one or another of the four participants in the equilibrium would absorb in a region of the visible or near-ultraviolet spectrum where none of the other participants had significant absorption.

Some of these equilibrium constants have been reported previously.[7] The present paper nearly doubles the number of values available and improves several of the earlier values, as well as describing the methodology.

In the course of these measurements we found it necessary to also measure equilibrium constants, K_R, for a number of reactions of the type shown in eq 2.[8] In our

$$A_i^+ + ROH \rightleftharpoons A_iOR + H^+ \qquad (2)$$

present solvent mixture R may be either H or i-C_3H_7. While we believe that the A_iOR are, for the most part, A_iOH, we have not attempted to distinguish between alcohols and ethers, and the K_R values reported are actually composites, given by eq 3. They were determined by a standard spectrophotometric procedure.[9]

$$K_R = \frac{[(A_iOH) + (A_iO\text{-}i\text{-}C_3H_7)](H^+)}{(A_i^+)} \qquad (3)$$

Compound **5H** is the conjugate base of a Brønsted acid. The dissociation constant of the acid was also determined spectrophotometrically.[9]

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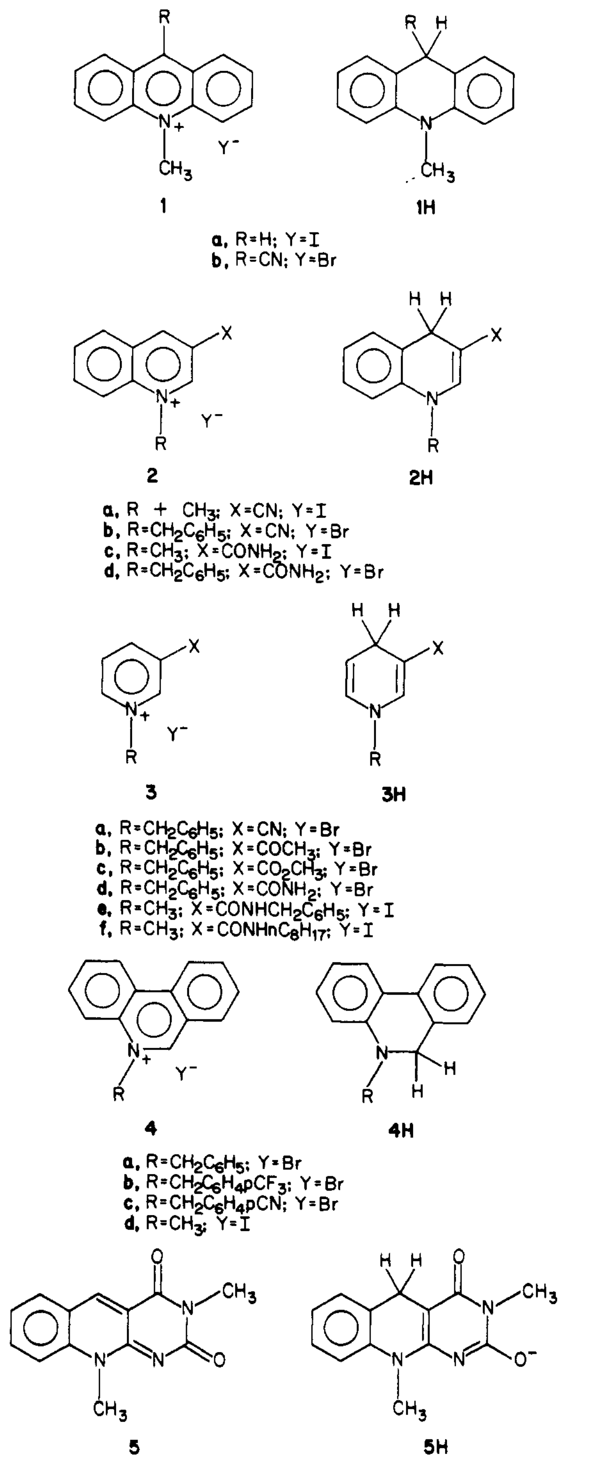
Chart I



Wherever an equilibrium resulted in the net formation or discharge of ions, ionic activity coefficients γ were introduced at the appropriate place in the equilibrium expression. They were estimated using the Debye–Hückel formula, eq 4.[10] The sum of the ionic radii was assumed

$$\log \gamma = -1.87\mu^{1/2}(1 + 4.05\mu^{1/2})^{-1} \qquad (4)$$

to be 8 Å by analogy with somewhat similar ions.[11] The ionic strength is μ. The dielectric constant of the mixed solvent was estimated to be 33, by interpolation.[12,13]

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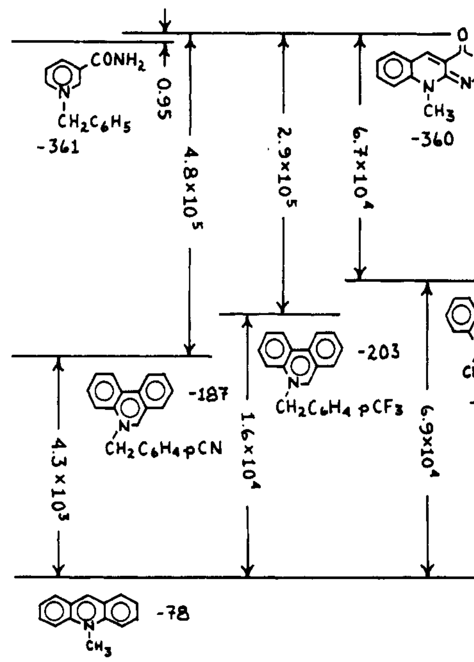

Figure 1. Outline of the indirect determination of the equilibrium constant for the reduction of **1a** by **5H**. The values shown between horizontal lines are measured equilibrium constants. Each pair of measured values yields a value of the overall equilibrium constant by multiplication. The average of the three overall values, 3.7×10^9, was taken as the best value for the overall equilibrium constant. The estimated standard reduction potentials of the cation vs. the standard hydrogen electrode is also shown with each structure.

Table I. Equilibrium Constants for Reduction of 1a by NADH Analogues and Reduction Potentials of Corresponding Cations

reductant	reference oxidant	measured k_+,[a] $M^{-1}\,s^{-1}$	measured K	K vs. 1a	$-E^0$,[b] mV
1Ha	–		–	1.00	78
1Hb	**2b**	7.3×10^{-5}	2.4×10^{-2} [c]	1.1×10^{-3}	−8
2Ha	**1a**	2.1×10^{-2}	1.4[d]	1.4	83
2Hb	**1a**	2.0×10^{-3}	4.5×10^{-2} [d]	4.5×10^{-2}	39
2Hc	**1a**	6.8×10^{-1}	2.2×10^{3} [d]	2.2×10^{3}	177
2Hd	**1a**	8.8×10^{-1}	4.9×10^{2} [d]	4.9×10^{2}	158
3Ha	**5**	1.23×10^{-4}	1.6×10^{-5}	6.0×10^{4}	220
3Hb	**4a**	1.46×10^{-2}	9.1×10	6.3×10^{6}	280
3Hc	**5**	$1.3. \times 10^{-2}$	1.0×10^{-2}	3.9×10^{7}	303
3Hd	**5**	3.4×10^{-2} [e]	9.5×10^{-1} [d]	3.4×10^{9}	(361)[f]
3He	**5**	4.7×10^{-1}	7.3×10 [d]	2.7×10^{11}	417
3Hf	**5**	4.7×10^{-1}	9.0×10 [d]	3.3×10^{11}	420
4Ha	**1a**	4.6	6.9×10^{4} [d]	6.9×10^{4}	222
4Hb	**1a**	1.68	1.6×10^{4}	1.6×10^{4}	203
4Hc	**1a**	1.07	4.3×10^{3}	4.3×10^{3}	187
4Hd	**5**	1.04×10^{-2}	5.5×10^{-4}	2.0×10^{6}	265

[a] Since K was evaluated as k_+/k_-, k_- is k_+/K. [b] Reduction potential in water of the cation corresponding to the reductant. [c] Measured at a pH of 3 because of the sensitivity of **1b** to basic hydrolysis. [d] These K's have been reported previously. Some of the present values are the same as those reported previously;[7,9] in other cases the values have been changed, in one case (**2a**) by a little over a factor of 2. In all cases where the new values differ from the old, we prefer the present values. [e] Average of the value, 3.2×10^{-2}, obtained from eq 8, and 3.7×10^{-2}, obtained from eq 11. [f] Assumed.[14–16]

A correlation between log K and log K_R values was found for structurally related compounds, but it is not general. Values of log K are also correlated with a sum of estimated polar and resonance effects.

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Table II. Pseudo-Acidity of NAD^+ Analogues

cation	pK_R
1	7.74
2b	5.31
4a	8.78
4b	8.03
4c	7.79
4d	9.66

Results

The determination of the equilibrium constant for reduction of **1a** by **5H** is outlined in Figure 1. A best value of 3.7×10^9 was obtained by taking the mean of the three combinations. The average deviation from this mean is 1.1×10^9, which is consistent with the estimated uncertainty, of about 10%, in the indiviudal, measured equilibrium constants. The best value of the K for **5** is probably uncertain by ~15%.

Values of K are reported in Table I, along with the reference compound against which they were measured, and estimates of the reduction potentials, E_0, of the cations in water. Values of K which were directly measured by reaction with **1a** and **1Ha** are throught to be uncertain by ~10%. Those which were measured with the aid of a secondary reference reflect any error in the K value, of the reference as well, and are uncertain by ~25%.

The reduction potential of **3d** against the standard hydrogen electrode was assumed to be −361 mV.[14,15] Other standard reduction potentials were evaluated relative to this value by means of eq 5, where $\mathcal{F}$ is the Faraday constant and n, the number of electrons transferred, is two in this case.

$$RT \ln K = n\mathcal{F}\Delta E° \qquad (5)$$

The values of K, but not the E^0 values, are assumed to be the same in our solvent as in water. The E^0 values refer to water. In addition to the uncertainty in the K values, the E^0 values bear the uncertainty in the reference value for **3d**. We are not able to estimate the possible error due to our assumption of solvent invariance for K, but we note this assumption is common in this field.[14,15] The error in E^0 due to a 10% error in K would be 1.3 mV; for 25% it would be 3.1 mV.

Mean values of pK_R are given in Table II. Each was determined from 4–25 separate determinations of spectra and solution pH values. The average deviation from the mean varied from 0.02 to 0.06. The standard error of the mean values varied from 0.01 to 0.02. These uncertainties are roughly consistent with the reproducibility of pH measurements (±0.3) and spectral intensities (±1%). Since we are not aware of any systematic errors in these measurements, we believe that the standard errors of the pK_R values accurately represent their uncertainty.

The acid dissociation constant, K_{HA}, of the conjugate acid of **5H** was determined by the same spectrophotometric technique as the K_R values. Sixteen determinations gave an average pK_{HA} of 8.60 with an average deviation from the mean of 0.04 and a probable error of 0.01 for the mean value.

Discussion

The general trend of the values in Table I is about as expected. Electron-withdrawing substituents make K for the reduction of **1a** smaller. Increasing the π-electron localization energy in the aromatic cation makes K larger.

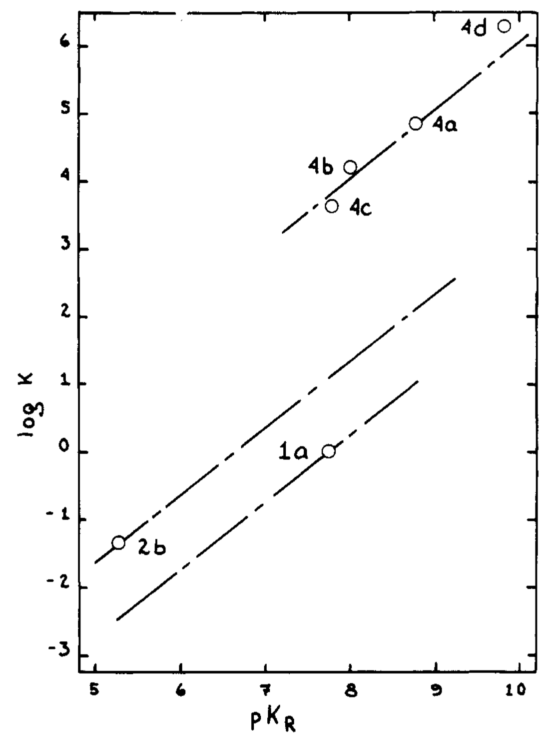

Figure 2. Relation between log K and pK_R. The compounds generating the points are identified. Th dot–dash lines have unit slope. If eq 5 was a completely satisfactory model for eq 1, all the points would fall on a single line of unit slope, so the vertical deviation of a point from the line through **1a** is a measure of the failure of that model.

For **3a–d**, values of log K are a roughly linear function of the Hammett σ's[17] with a slope of −12. After the effect of substituents at the 3-position was allowed for with a ρ of −12, and a δ of 1.2 was subtracted from the log K values of 1-methyl derivatives to estimate the values for the corresponding benzyl derivatives, a linear relation was obtained between log K and the change in the Hückel localization energy for addition of hydride to the corresponding aromatic hydrocarbon,[18] with a slope of 25.6. These correlations can be summarized in eq 6, which reproduces 10 of the log K values, ranging from −1.35 to 9.54, with an average discrepancy between calculated and observed values of 0.6.

$$\log K = -12\sigma + 25.6(\Delta \mathrm{LE}) + \delta \qquad (6)$$

Five of the reducing agents have structural features that are not taken account of in eq 6, so their K values could not be used in this correlation. The moderate success of eq 6 suggests that polar and resonance effects on these equilibria are separable and can be approximately estimated in simple semiempirical ways.[19] Nevertheless the effect on log K of replacing methyl with benzyl at the 1-position varies from −1.5 log units to −0.65 log unit in the present work, and values of −1.4 units and −0.1 unit can be obtained from Table I of Kellogg and Piepers.[14] Also, the coefficient of ΔLE in eq 6 can be used to estimate a value of −35 kcal mol^{-1} for the Hückel β, which is considerably more negative than the conventional value of about −20 kcal mol^{-1}.[20] These difficulties limit, but do not abolish, the predictive power and theoretical significance of eq 6.

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It might be hoped the K values could be modeled by values of K' (eq 7). We have shown[9] that such a model

$$Ac^+ + A_iOH \rightleftarrows AcOH + A_i^+ \quad (7)$$

would give a good approximation of relative K values in a series of meta- and para-substituted benzylquinoline derivatives. Figure 2 indicates that their absolute values would be discrepant by a factor of about 10. Relative K values would also be reasonably approximated for phenanthridine derivatives; however, absolute values are larger than those that would be estimated by a factor of $\sim 10^4$. It follows that the model can only be used with confidence for comparing K values generated by derivatives of the same ring system. The same caveat probably applies to the cyanide affinity method for determining K values.[16]

If the assumption of invariance of K with solvent[14] can be accepted, the present E^0 values can be combined with a considerable number of previously available values[14-16,21] to give a sizeable body of equilibrium constants. However the conventional tabulation[22] contains values of heterogeneous origin. Sometimes the nature of the half-reaction is not known. Therefore, in general, such combinations and comparisons should be made with caution. The values selected and reported by Kellogg and Piepers[14] all appear to reliably refer to hydride transfer equilibria, and, apart from the discrepancies due to solvent, to be comparable with the present values.

Experimental Section

Materials. 10-Methylacridinium iodide (**1a**) and 5-methylphenanthridinium iodide (**4d**) were prepared from the corresponding free bases (Aldrich Chemical Co.) and a 3-fold excess of methyl iodide in the minimum volume of acetone required to dissolve the bases. These solutions were maintained at room temperature for 2 days, during which time the products separated spontaneously, as crystalline solids. They were recrystallized from 4:1 ethanol-water, and both melting points agreed with those previously reported,[23,24] as did the electronic spectrum of **1**.[25] The yields of recrystallized material were about 80%.

The 3-substituted benzylpyridinium bromides, **3a-d**, were prepared from the corresponding 3-substituted pyridine (Aldrich Chemical Co.) and a 1.5-fold excess of benzyl bromide by refluxing in anhydrous ethanol for 3-6 h. The products usually separated spontaneously as crystalline solids when the reaction mixture was cooled. If they did not, a little ethyl ether was added to induce separation. The crude products were recrystallized from anhydrous ethanol. Yields were 70-80%. Our preparations of **3a-d** had melting points within a few degrees of those previously reported.[26-28]

3-((Benzylamino)carbonyl)-1-methylpyridinium iodide (**3e**) and 1-methyl-3-((octylamino)carbonyl)pyridinium iodide (**3f**) were prepared from methyl iodide and the free bases, as described above for **1** and **4d**. They were recrystallized from anhydrous ethanol. **3e** had a melting point of 136-138 °C. Its electronic spectrum had λ_{max} values, with log ϵ_{max} values in parentheses, of 266 (3.73) and 218 (4.37) nm. **3f** had a melting point of 117.5-118.5 °C λ_{max} values of 265 (3.77) and 216 (4.40) nm. The two 3-((alkylamino)carbonyl)pyridines were prepared by refluxing a solution of nicotinic acid and an excess of the alkylamine in xylene and trapping and removing the water as it was formed.[29] They were recrystallized from ethanol and had melting points within 1 °C of those previously reported.[29,30]

The three 5-benzylphenanthridinium bromides, **4a-c**, were prepared from phenanthridine and a 1.2-fold excess of the corresponding benzyl bromide. Phenanthridine (3 g, 17 mmol), the benzyl bromide, and $\sim$2.5 cm^3 of methanol were heated together in a sealed tube at 100 °C for 1-2 h. On cooling, the products separated as solids, which were recrystallized from methanol. Yields were 70-80%. The melting point of **4a** was within 1 °C of the previously reported value.[31] There are no previous reports of **4b** or **4c**. They had melting points of 240-244 °C dec and 247-249 °C dec, respectively. The λ_{max} values and log ϵ_{max} values (in parentheses) of the electronic spectra of these compounds in 4:1 2-propanol-water are as follows: for **4a**, 364 (3.61) and 324 (3.89); for **4b**, 364 (3.61) and 328 (3.85); and for **4c**, 365 (3.64) and 324 (3.95).

To prepare 3,10-dimethyl-5-deazaisoalloxazine (**5**), 10-methyl-5-deazaisoalloxazine, prepared by the method of Yoneda,[32,33] was suspended in a small volume of methanol, and 10% aqueous NaOH was added dropwise, with stirring, until the suspended material all dissolved. A 3-fold excess of methyl iodide was added to this solution, and the mixture was allowed to react at room temperature. The product that precipitated was collected by filtration and washed with a small amount of methanol and then with a small amount of cold water. It was dried under vacuum for 2 days, and then had a melting point of 326 °C dec. Yoneda reports 327 °C.[32] It had NMR (Me_2SO-d_6), IR, and electronic spectra suitable to its structure.[34]

10-Methylacridan (**1H**) and the 5-substituted phenanthridans **4Ha-d** were prepared by reducing the corresponding acridinium or phenanthridinium salts with $NaBH_4$. Three-gram portions (about 10 mmol) of the salts were dissolved in 200 cm^3 of a 2:1 methanol-water mixture and cooled to 10 °C. To each of these solutions was added, dropwise, 0.4 g (10 mmol) of $NaBH_4$ dissolved in 10 cm^3 of water. The products separated promptly and spontaneously. To lower the solubility of the products in the solvent a further 200 cm^3 of water was added, and 10-cm^3 portions of dichloromethane were added to facilitate the separation of the products from the resulting large volumes of methanol-water. After separation of the layers, the dichloromethane was removed under vacuum, with evaporation encouraged by a water bath at or below 40 °C, leaving solid or semisolid crude products. These were purified by crystallization from methanol, to which small amounts of water were added. Yields were between 70 and 80%. **1H** and **4Hd** had melting points within 2 °C of those previously reported.[24,25] There are no previous reports of **4Ha-4Hc**. They had melting points of 106, 89-90, and 131-133 °C, respectively. Their electronic, IR, and NMR spectra were suitable to their structures.[34]

The 1,4-dihydropyridines, **3Ha-f**, were prepared by reducing the corresponding pyridinium salts with $Na_2S_2O_4$.[35] **3Ha** and **3Hd** had melting points identical with those previously reported.[27,35] Our sample of **3Hb** had mp 65-67.5 °C, compared to 61-67 °C previously reported.[37] However our sample of **3Hc** had mp 44-46 °C, compared to 90-91 °C previously reported.[37] Its IR and NMR spectra were those expected for its structure and very similar to those of other members of the series. Its electronic spectrum was also similar to the others, and had its long wavelength λ_{max}, with log ϵ_{max} in parentheses, at 355 nm (3.86), compared to 353 nm (3.86) which has been reported.[37] We are unable to explain the discrepancy between the two melting points. There are no previous reports of **3He** and **3Hf**. The former had mp 84-85 °C; the latter is an oil. Both had IR, NMR, and electronic spectra consistent with their structures.[33] The long wavelength λ_{max} and ϵ_{max} values of **3He** and **3Hf** were indistinguishable from those of **3Hd**.

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1,5-Dihydro-3,10-dimethyl-5-deazaisoalloxazine (**5H**) was prepared by adding an excess of $NaBH_4$ to a solution of **5** in a minimum of methanol. After a similar volume of water was added and most of the methanol was evaporated, the solution was acidified with glacial acetic acid and the product precipitated. The product was washed with a minimum volume of cold water. It could not be usefully recrystallized. It had mp 305–310 °C dec, after initially turning brown at 270 °C. It has been reported to melt at 278 °C.[31]

9-Cyano-10-methylacridan (**1Hb**) was prepared by addition of KCN to an aqueous solution of **1a** by the method of Kaufmann and Albertin.[38] To avoid byproduct resin formation it was necessary to add ether to the aqueous solution of **1a** before adding the aqueous KCN and to agitate the mixture vigorously during addition, so that the product would be removed as it was formed. The product, formed in 80% yield, had mp 141–142 °C; 143 °C was originally reported.[38] Our material had λ_{max} 275 nm (log ϵ_{max} 4.18). A value of 278 nm (3.90) has been reported,[39] but for a material that melted at 110–112 °C, and may have been heavily contaminated.

To prepare 9-cyano-10-methyl-acridinium bromide (**1b**) 6 g of **1Hb** was mixed with 300 cm^3 of CCl_4, in which it did not completely dissolve. An excess of Br_2 was added, and 8 g of product separated immediately. This could be recrystallized from an acidified 4:1 mixture of 2-propanol and water. Finally it was washed with CH_2Cl_2 (60% recovery). This material showed a band at 3400 cm^{-1} in its IR spectrum, and its analysis agreed with theory for $^1/_2$ mol of water per mol of **1b**. The melting point of **1b** was 210 °C dec and its electronic spectrum had λ_{max} (log ϵ_{max}) at 481 (3.45), 451 (3.63), 426 (3.58), 386 (4.38), 368 (4.06), and 264 nm (4.99). A compound reported as the nitrate of **1b**[39] gave λ_{max} values of 386, 368 and 264 nm, but with ϵ_{max} values uniformly $\sim ^1/_4$th of the present ones. We believe it was probably a very impure sample. It was prepared from a **1Hb** preparation which we also believe was impure (vide supra). The structure of the present compound is confirmed by its IR and NMR spectra, which are very similar to those of **1a**.

The preparation and properties of the quinoline derivatives, **2a–d**, and dihydroquinoline derivatives, **2Ha–d**, have been previously described.[40]

Satisfactory elemental analyses for C, H, and N were obtained for compounds **1b**, **3e**, **3f**, **3He**, **3Hf**, **4b**, **4c**, **4Ha–4Hc**, and **3Hc**; none of the experimental percentages differed from the theoretical by more than 0.3%.

$NaBH_4$ was purchased by Baker Chemical Co., originally specified 98% active. This material is very hydroscopic, ultimately forming a solid dihydrate. The real $NaBH_4$ content of reaction mixtures must be considered somewhat lower than their nominal content, in spite of the usual precautions to avoid contact with moisture. In our hands analysis of $NaBH_4$ has generally shown 90–95% activity. $Na_2S_2O_4$ was purchased from Matheson Coleman and Bell and was of Practical grade.[41] No better grade of this material is available. It is generally contaminated with a variety of partially oxidized materials. Both $NaBH_4$ and $Na_2S_2O_4$ were used as supplied. Other reagents and solvents were obtained from standard sources and were of analytical reagent grade.[41]

Methods. Rate and equilibrium constants were determined spectrophotometrically. Reacting solutions were kept in the cell compartment of a spectrophotometer, shielded from light, with the temperature maintained at 25.0 ± 0.2 °C by pumping water from a thermostat through the compartment jackets. The temperature was periodically measured in a cuvette in which absorbence was not being monitored.

Pseudo-first-order rate constants for reactions that would almost entirely consume one of the reactants were obtained by using eq 8.[42] The symbols have their usual significance. Second-order rate constants, k_+ or k_-, were given, for reactions not involving **5H**, by k_1/b, where b is the concentration of the reactant which is in excess. For such reactions the limiting concentration was around 10^{-4} M, and b was always larger than the limiting concentration by at least a factor of 15, usually by a factor of 20 or more. Except for the reaction of **2b** with **1Hb**, the pH was maintained around 5 by a very low ($\sim 10^{-3}$ M) concentration of an acetic acid–acetate buffer. For the reaction with **2b** the pH was maintained at around 3 because of the sensitivity of **2b** to base-catalyzed hydrolysis. At the pH's used for these reactions the spectra of products and reactants in separate solutions did not change detectably over the time periods required by the reactions, and no significant fraction of any of the oxidizing agents is hydroxylated. At least four separate experiments, with at least a 4-fold variation in b, were performed to determine k_+ or k_-. When **5H** was not a reactant, the average deviation from the mean value was around 4% and the probable error of the mean, about 1.5% of the mean. The largest probable error was 3%.

$$k_1 = t^{-1} \ln [(A_0 - A_\infty)/(A_t - A_\infty)] \tag{8}$$

Table III. Iterative Determination of k_- and K[a]

$10^{-4}K$ (est.)[b]	$10^5 X_e$	$10^6 k_-$	$10^{-4}k_+/k_-$[c]
6.56	1.38	5.77	8.02
7.40	1.30	5.90	7.85
8.14	1.24	6.07	7.63
7.76	1.27	5.97	7.76

[a] For the reaction of 1.6×10^{-2} M **1aH** with 8.0×10^{-4} M **4a**. [b] Input values of K, selected subjectively. [c] Output values of K.

Since **5H** is in rapid equilibrium with its conjugate acid, k_1 values for reactions in which it is a reducing agent could be brought into a convenient range by adjusting the pH. In the present case acetic acid–acetate or boric acid–borate buffers were used to get pH's between 4.5 and 9. Values of k_+ or k_- were given by $k_1/bpq\gamma^2$. The fraction of **5H** present as the reactive anion, p, is given by eq 9. The negative log of the measured pH, which is approximately the activity of H^+, was h. At these pH's the oxidizing agents were partially hydroxylated. The fraction unhydroxylated, which was always >0.5, is given by q, and evaluated according to eq 10. Values of γ^2 were typically ~0.6 and occasionally as low as 0.4. Values of k_+ and k_- involving **5H** as a reactant showed substantially more scatter than others, partly due to errors in k, and partly to the greater sensitivity of these reactions to the solvent composition. A typical example is the reaction of **5H** (5×10^{-5} M) with **4b** ($1.3\text{–}3.7 \times 10^{-3}$ M). Eleven values of k_1 were obtained, at pH values from 5.9 to 7.6. The mean value of k_+ was 3.4×10^2 M^{-1} s^{-1}, with an average deviation of 1.0×10^2 and a probable error of 0.3×10^2. The largest probable error in a k_+ or k_- value determined this way was 11% of the mean and a typical probable error was 6%.

$$p = K_{HA}(K_{HA} + \gamma h)^{-1} \tag{9}$$

$$q = h(K_R\gamma + h)^{-1} \tag{10}$$

For reactions which came to equilibrium with substantial amounts of both reactants still present, k_1 was evaluated using eq 11.[43] The initial concentration of the limiting reactant is a, x_e is the (equal) concentration of the two products at equilibrium, and x_t is the concentration of the products at time t. Unlike eq 8, eq 11 requires that actual concentrations be known at each t. These were determined from the known initial concentrations, the known molar absorbances, and a measured absorbance at a wavelength above 420 nm, where absorbance is entirely due to **1** or **5** in the present experiments. Since eq 12 was never used for reactions of **5H**, k_- values were always given by k_1/b when the k_1 values were determined from eq 11. A value of K is also required, in order to calculate x_e. In reactions not involving **5**,

$$k_1 = \left(\frac{x_e}{2a - x_e}\right) t^{-1} \ln \left[\frac{a x_e + x_t(a - x_e)}{a(x_e - x_t)}\right] \tag{11}$$

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where k_+ was relatively secure, an iterative procedure was used. First K was estimated from the measured absorbances. Then k_- was calculated from eq 1. A new value of K was given by k_+/k_-. This process was repeated until input and output K values differed by less than 1%. Usually no more than three calculations of k_- was required to meet this criterion. Table III shows the course of a typical iteration. For reactions involving **5**, where the k_+ values were less secure, the iterative procedure was not used in order to avoid compounding the error in k_+. Fortunately, these reactions were faster than others, and satisfactory approximations of K could be obtained from the absorbances at 10 or more half-lives. Nevertheless, values of K given by k_+/k_- were judged to be more reliable than those obtained from final absorbances and are the values reported in Table I. In no case did the two values of K differ by more than 50%, and typical discrepancies were around 25%. On replication, values of K and k_- determined by eq 11 typically showed an average deviation from the mean of ~10% and a probable error ~4%. The largest probable error in these constants was 6%. When possible systematic errors are also considered (errors in k_+ and K_R), it seems reasonable to assign an uncertainty of ±10% to the K values. For reaction of **5** with **3Hd** and the reverse it was possible to measure k_1 both in pseudo-first-order (eq 8) and in second-order (eq 11) conditions, by suitably adjusting the concentration of **3Hd** or **3d**. The values of k_+ were 3.18 and 3.66×10^{-2} M^{-1} s^{-1}, from the pseudo-first-order and the second-order experiments, respectively, and for k_-, 3.48 and 3.66×10^{-2} M^{-1} s^{-1}. The discrepancies between these values are entirely consistent with the uncertainties estimated above.

All values of k_1 were fitted to the data using a linear least-squares program in a programmable calculator. The correlation coefficients were all above 0.99. The absence of curvature was verified graphically. In a few cases the average discrepancy between measured absorbances and those calculated from eq 8 or 11 was calculated, by using the determined values of the constants. This was less than 0.001 in each case. Thus the scatter in the constants originates in such factors as temperature control or pH measurement, rather than inaccuracies in absorbances or the bias of the linear least-squares evaluation of k_1.

Values of pH were determined using a Radiometer pH meter with a glass pH electrode and a calomel reference electrode. The glass electrode was calibrated by using dilute perchloric acid solutions in the 2-isopropanol–water mixed solvent.

Absorbance was measured at a fixed wavelength using a hybrid spectrophotometer: the monochromator of a Beckman DU spectrophotometer with Gilson source, detector, and digital readout.

Nitration of Bis(amido)naphthalenes[1]

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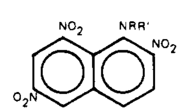
Nitration studies have been conducted on the bis(acetamido), bis(*p*-toluenesulfonamido), and bis(trifluoroacetamido) derivatives of 2,6-diamino-4,8-dinitro- and 1,5-diaminonaphthalene. The bis(trifluoroacetamides) were nitrated readily to produce tetranitro derivatives, whereas the *p*-toluenesulfonamides and acetamides gave predominantely dinitro products. The tetrakis(trifluoroacetyl) and tetraacetyl derivatives of 1,3,5,7-tetraaminonaphthalene were nitrated to yield di- and mononitro products, respectively. Solvolysis of some of the amides was successful (most facile with trifluoroacetamido), leading to the first preparations of 2,6-diamino-1,4,5,8-tetranitro-, 1,5-diamino-4,8-dinitro-, and 1,5-dinitro-2,4,6,8-tetraaminonaphthalenes. Peracid oxidation of the new diamines or amides failed to yield polynitronaphthalenes. The effect of structure on the course of nitration, solvolysis, and oxidation of the new nitrated naphthalene derivatives is discussed.

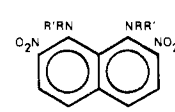
Introduction

As part of our investigation of synthetic routes leading to new polynitronaphthalenes, we have studied the nitration of selected bis(acetamido)-, bis(*p*-toluenesulfonyl)-, and bis(trifluoroacetamido)naphthalenes. These studies have led to the synthesis of some new polynitronaphthalenediamines. Synthetic methods leading to these materials are discussed as well as results of some unsuccessful attempts to convert them into hexa- and octanitronaphthalene. Of the 75 possible nitronaphthalenes, none are known which contain more than four nitro groups, nor are any such derivatives known, with the exception of 3,4,5,6,8-pentanitroacenaphthene.[3] The extensive studies by Hodgson[4] and Ward[5] and co-workers describe syntheses and structure assignments of many polynitronaphthalenes and their amino derivatives.

Nitrations of bis(amido)naphthalenes have been described by others. Two tetranitronaphthalenediamines and their derivatives have been reported[4a,6]—1,5-diamino-2,4,6,8-tetranitronaphthalene (**1a**) and 1,8-diamino-2,4,5,7-tetranitronaphthalene (**2a**). These compounds



1a; R = R' = H
1b; R = H, R' = 4-$CH_3C_6H_4SO_2$
1c; R = H, R' = 3-$NO_2C_6H_4SO_2$



2a; R = R' = H
2b; R = H, R' = 4-$CH_3C_6H_4SO_2$
2c; R = R' = CH_3

were obtained by nitration of the *N,N'*-bis(*p*-toluene-

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