Mechanism of Pseudobase Disproportionation. Kinetics and Mechanism of the Reaction of the Pseudobases of 2-(Substituted-benzyl)-5-nitroisoquinolinium Cations with the 2-Methylisoquinolinium Cation[1]

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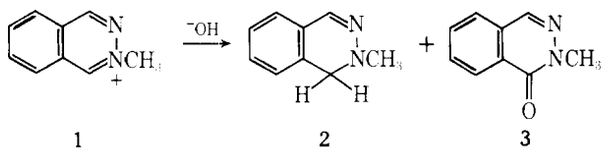
The rates of reaction of a series of 2-(X-benzyl)-5-nitroisoquinolinium cations (**8**, X = 4-CH_3O, 4-CH_3, H, 3-F, 3-CN, 4-CN) with the 2-methylisoquinolinium cation (**9**) to give the corresponding 2-(X-benzyl)-5-nitro-1-isoquinolinones and 1,2-dihydro-2-methylisoquinoline have been studied in 0.01–0.5 M KOH in 20% acetonitrile–water at 25 °C and ionic strength 1.0. These reactions are strictly first order in each reactant, and the dependence of the second-order rate constant on [$^-$OH] indicates that the reaction involves hydride transfer from the pseudobase anions of 8 to **9**. The correlation line for the pH-independent second-order rate constant, $\log k_2^H = -0.11\sigma + 1.35$, indicates that the transition state is quite "reactant-like". The rates of reaction of the corresponding 1-deuterio-2-(X-benzyl)-5-nitroisoquinolinium cations (**14**, X = 4-CH_3O, H, 3-F, 4-CN) have also been investigated ($\log k_2^D = -0.29\sigma + 1.13$). An X-dependent primary kinetic isotope effect is shown to be consistent with a reactant-like transition state for direct hydride transfer from C-1 of the *N*-benzyl-5-nitroisoquinoline derivatives to **9**. Such direct hydride transfer is confirmed by ^{1}H NMR spectral studies of the reaction of **8** with **9** in D_2O and of **14** with **9** in H_2O. The mechanism of the general disproportionation reaction of heterocyclic pseudobases is discussed in the context of the observed mechanism for the current reaction which can be considered as a "crossed disproportionation".

The disproportionation of heteroaromatic cations in aqueous base has been known for many years.[2-4] For example, fresh organic extracts of basic aqueous solutions of the 2-methylphthalazinium cation (**1**) contain[2,6,7] a mixture of 2-methyl-1,2-dihydrophthalazine (**2**) and 2-methyl-1-phthalazinone (**3**). Similar reactions have been reported for pyridinium,[7] isoquinolinium,[8,9] benzothiopyrylium,[10] quinazolinium,[11] acridinium,[3] xanthylium,[12] thioxanthylium,[12,13] and phenanthridinium[3] cations. In all cases, the cations display spectral changes consistent with pseudobase formation at electronic absorption spectral concentrations (e.g., 1 + $^-$OH ⇌ **4**),[6] with the disproportionation reaction becoming important only at much higher concentrations of the heterocycle. This concentration dependence indicates the bimolecular nature of these reactions, and the 1:1 ratio of oxidized and reduced products, in those cases which have been carefully investigated, is indicative of a true disproportionation reaction.



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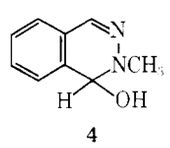

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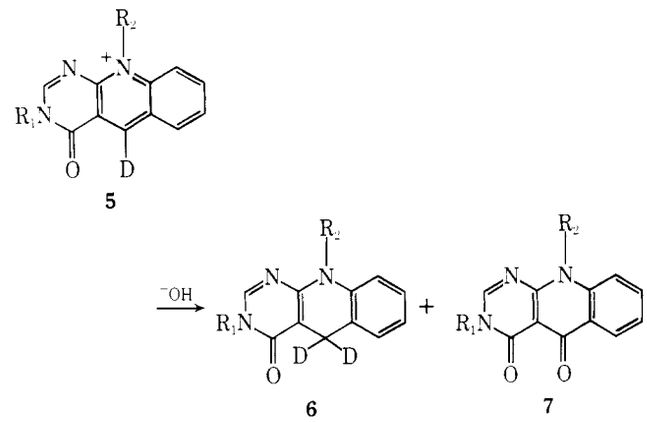
The bimolecular nature of the reaction has also been established[14,15] by deuterium labeling experiments in the case of the pyrimido[4,5-*b*]quinolinium cations **5**. Reduced product **6** is doubly labeled with deuterium; no deuterium is incorporated into the reduced product when the unlabeled cation is allowed to disproportionate in D_2O. Clearly, hydrogen transfer during disproportionation occurs without exchange with solvent protons, and so direct interaction between two heterocyclic molecules is indicated.

Disproportionation for the 2-methylphthalazinium cation occurs only in the range pH 10–13, with the pseudobase, itself, being extracted from more basic aqueous solutions in which the pseudobase alkoxide ion ($pK_{RO^-} = 13.0$) predominates.[6]



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Although there does not appear to have been a detailed kinetic study of the pH dependence of these disproportionation reactions, these qualitative observations suggest that the rate of disproportionation reaches a maximum value at the pH at which the concentration of the pseudobase is at its maximum value. At first glance, this result seems to suggest that the alkoxide ion is stable toward disproportionation and that this reaction proceeds via the pseudobase itself in aqueous solution but not in organic solvent. However, this interpretation is not consistent with the observed stability of many pseudobases to disproportionation, and it is difficult to conceive of a mechanism for a disproportionation via two molecules of the pseudobase. A kinetically equivalent mechanism for the reaction of two molecules of the pseudobase is the reaction of the pseudobase alkoxide ion with the heterocyclic cation as has been suggested[16] for the disproportionation of the pseudobase of berberine to oxyberberine and dihydroberberine.

Direct spectrophotometric kinetic studies of such disproportionation reactions are difficult because of the relatively high concentrations of heterocycle that are necessary to promote disproportionation and the relative insolubility of both reaction products in aqueous media. For an investigation of the kinetics and mechanism of such reactions, we have chosen to study the "crossed disproportionation" reaction between 2-benzyl-5-nitroisoquinolinium cations (**8**) and the 2-methylisoquinolinium cation (**9**) which react in aqueous base to give the 2-benzyl-5-nitro-1-isoquinolinones (**10**) and 1,2-dihydro-2-methylisoquinoline (**11**). Such a crossed reaction

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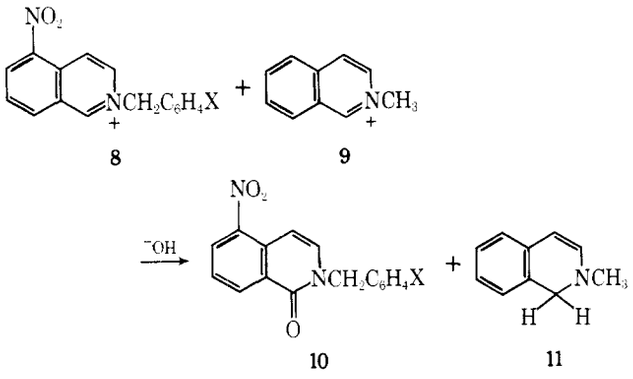
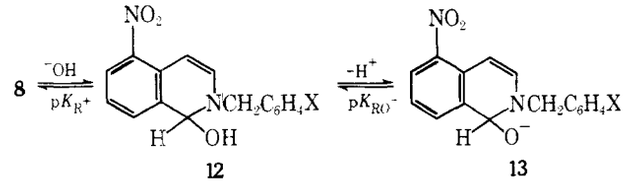


also has the advantage that one can study substituent effects (e.g., X in 8) in the two reacting species individually; the interpretation of substituent effects in a simple disproportionation is complicated by simultaneous substituent variation in both reacting species. The present paper reports a kinetic study of the mechanism of the above reaction via pH–rate dependence, substituent effects, and kinetic isotope effects.

Results

Basic aqueous solutions of 2-benzyl-5-nitroisoquinolinium cations (8) are pink due to the presence of the pseudobases **12** (λ_{max} 450–458 nm) and/or the pseudobase anions **13** (λ_{max} 493–507 nm).[17] Quantitative studies[17,25] of cation–pseudobase equilibration in these systems indicate that the cations 8 are essentially completely converted to their pseudobases **12** at



even the lowest base concentrations (0.01 M KOH) investigated in the current kinetic study. Addition of the 2-methylisoquinolinium cation to such pink solutions ([KOH] = 0.01–0.5 M) produces decolorization at rates which can be conveniently measured by conventional spectrophotometry at room temperature. The time dependence of the visible absorption spectrum of the 2-(4-methoxybenzyl)-5-nitroisoquinolinium cation in 0.5 M KOH in the presence of excess 2-methylisoquinolinium cation is displayed in Figure 1. The presence of a relatively clean isosbestic point at 413 nm is indicative of the occurrence of a single major reaction that does not involve intermediate species in any significant concentration. These spectral changes are consistent with the formation of 2-(4-methoxybenzyl)-5-nitro-1-isoquinolinone (**10**, X = 4-CH_3O) (λ_{max} 367 nm[17]) and 1,2-dihydro-2-methylisoquinoline ($\lambda_{max}(CHCl_3)$ 328 nm[6]) since neither of these products show more than a very weak tail absorption in the vicinity of 500 nm.

These two reaction products were confirmed by H^1 NMR spectral studies of chloroform extracts of a basic solution in which the 2-(4-cyanobenzyl)-5-nitroisoquinolinium and 2-methylisoquinolinium cations had been allowed to react under the conditions described in the Experimental Section. The product spectrum clearly indicated a mixture of **10**, X = 4-CN, and **11**. Repetition of this experiment in basic D_2O, and also the corresponding reaction of the 1-deuterio-2-(4-cyanobenzyl)-5-nitroisoquinolinium (**14**) and 2-methylisoquinolinium cations in H_2O, indicated that there was no detectable incorporation of solvent hydrogen at C-1 of the 1,2-dihydro-2-methylisoquinoline product. Thus direct transfer of hydrogen occurs from C-1 of the *N*-(4-cyanobenzyl)isoquinoline derivative to C-1 of **9**.

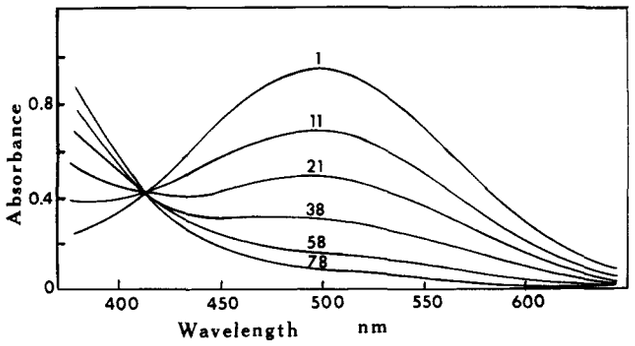


Figure 1. Time dependence of the absorption spectrum of a solution containing 8·Br^- (X = 4-CH_3O) (2.1×10^{-4} M) and 2-methylisoquinolinium bromide (1.7×10^{-3} M) in 0.5 M KOH in 20% CH_3CN–H_2O at 25 °C, ionic strength 1.0. Spectra were recorded at times (min) indicated on each curve.

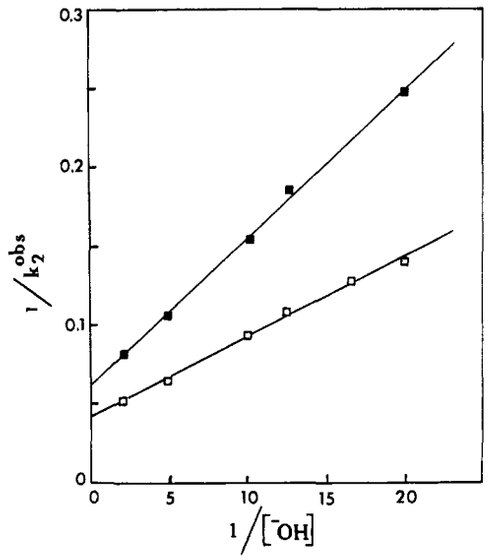
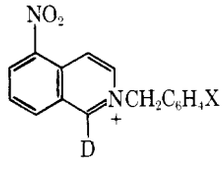


Figure 2. Double reciprocal plot of dependence of k_2^{obsd} on [$^-$OH] for 8·Br^- (X = 4-CH_3O) (□) and 14·Br^- (X = 4-CH_3O) (■). Data at 25 °C, ionic strength 1.0, in 20% CH_3CN–H_2O.



For each of the *N*-benzyl-5-nitroisoquinolinium cations 8 (X = 4-CH_3O, 4-CH_3, H, 3-F, 3-CN, 4-CN) the change in absorbance at 480 nm was recorded as a function of time in the presence of 50–500-fold molar excesses of 2-methylisoquinolinium cation in the range 0.01–0.5 M KOH in 20% CH_3CN in water at 25 °C, ionic strength 1.0. In all cases the reaction proved to be first order in the 5-nitroisoquinoline derivative for at least 4 half-lives and pseudo-first-order rate constants, k_1^{obsd}, were calculated. Values of k_1^{obsd} were proportional to the concentration of the 2-methylisoquinolinium cation, and thus the kinetics of the reaction are first order in each reactant. The second-order rate constant k_2^{obsd} was evaluated for each X at 6–10 base concentrations in the range [KOH] = 0.01–0.5 M. In each case, plots of $1/k_2^{obsd}$ vs. 1/[$^-$OH] were linear (e.g., Figure 2), and extrapolation of these plots to 1/[$^-$OH] = 0 gives $1/k_2^H$, where k_2^H is a second-order rate constant that is independent of [$^-$OH]. The values k_2^H that were evaluated in this way for each 8 from least-squares analysis of the plots in Figure 2 are given in Table I.

Table I. Kinetic Parameters for the Reduction of the 2-Methylisoquinolinium Cation[b] by *N*-Benzyl-5-nitroisoquinolinium Cations[a]

cation	X	registry no.	k_2^H, M^{-1} min^{-1}	k_2^D, M^{-1} min^{-1}	K, M^{-1}
8	4-CH_3O	64840-47-7	23.9 ± 0.2		8.3 ± 0.1
	4-CH_3	64840-46-6	23.1 ± 0.2		8.2 ± 0.1
	H	52166-52-6	22.9 ± 0.2		7.5 ± 0.1
	3-F	64840-45-5	20.7 ± 0.2		10.4 ± 0.1
	3-CN	64840-43-3	18.6 ± 0.4		12.7 ± 0.3
	4-CN	64840-42-2	19.5 ± 0.5		12.7 ± 0.3
14	4-CH_3O	64840-51-3		15.7 ± 0.3	6.8 ± 0.2
	H	64840-50-2		13.6 ± 0.3	7.8 ± 0.2
	3-F	64840-49-9		10.9 ± 0.2	12.8 ± 0.3
	4-CN	64840-48-8		8.5 ± 0.3	10.9 ± 0.3

[a] At 25.0 °C, ionic strength 1.0, 20% CH_3CN–H_2O. [b] Registry no. 33718-23-9.

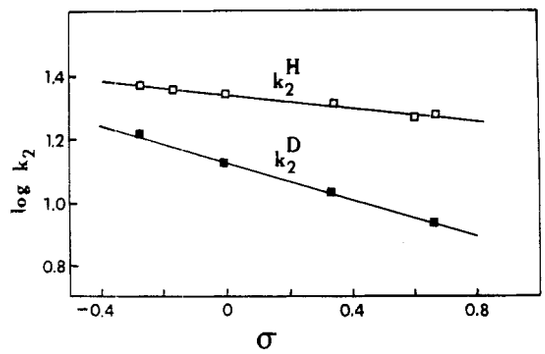


Figure 3. Hammett plots for the dependence of k_2 on X for 8 (k_2^H) and 14 (k_2^D).

The linear relationships in Figure 2 are consistent with eq 1, where K is the equilibrium constant for a rapidly established preequilibrium of the form

$$k_2^H = k_2^{obsd}(1 + 1/K[^-OH]) \quad (1)$$

$$K = [Y]/[Z][^-OH]$$

Values of K were evaluated from the slopes (= $1/k_2^H K$) of the lines in Figure 2 and are included in Table I. Since the 2-methylisoquinolinium cation is not involved in a base-dependent equilibrium in this region,[6] the equilibrium constant K must be related to a base-dependent equilibrium of the *N*-benzyl-5-nitroisoquinoline derivatives. In fact, it has been established that alkoxide ion (**13**) formation from the pseudobases (**12**) does occur in this region and values of K_d = [13]/[12][$^-$OH] for this ionization have previously[17] been evaluated spectrophotometrically under the current experimental conditions (except for the absence of the 2-methylisoquinolinium cation). Values of K = 7–12 M^{-1} in Table I are in reasonable agreement with K_d = 9–12 M^{-1} previously reported for these species.

The kinetics of oxidation of four *N*-benzyl 1-deuterio-5-nitroisoquinolinium cations **14** by the 2-methylisoquinolinium cation were also investigated in the same way as described above, and the values of k_2^D and K that were evaluated for these deuterated derivatives are also included in Table I.

In Figure 3, k_2^H and k_2^D are plotted as a function of the Hammett σ constant for the substituent X. Least-squares analysis gives the correlation lines of eq 2 and 3.

$$\log k_2^H = -0.11(\pm 0.04)\sigma + 1.35(\pm 0.01) \quad \text{(corr. coeff. = 0.977)} \quad (2)$$

$$\log k_2^D = -0.29(\pm 0.03)\sigma + 1.13(\pm 0.01) \quad \text{(corr. coeff. = 0.997)} \quad (3)$$

Table II. Kinetic Isotope Effects for the Reduction of the 2-Methylisoquinolinium Cation by *N*-Benzyl-5-nitroisoquinolinium Cations (8 and 14)[a]

X	k_2^H/k_2^D	X	k_2^H/k_2^D
4-CH_3O	1.52	3-F	1.90
H	1.68	4-CN	2.29

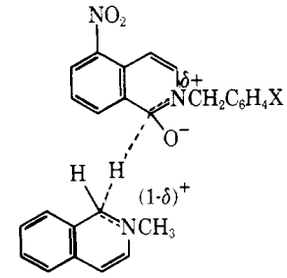
[a] At 25 °C, ionic strength 1.0, in 20% CH_3CN–H_2O.

The difference in the slopes of these correlation lines is significantly greater than the experimental error. In fact the kinetic isotope effect k_2^H/k_2^D shows a clear dependence on the electronic effect of the substituent X (Table II), and from eq 2 and 3 the substituent dependence of this isotope effect can be expressed by eq 4.

$$\log (k_2^H/k_2^D) = 0.18\sigma - 0.23 \quad (4)$$

Discussion

The reaction between the 2-benzyl-5-nitroisoquinolinium cation and the 2-methylisoquinolinium cation in aqueous base results in the oxidation of the former to 2-benzyl-5-nitroisoquinolinone and reduction of the latter to 1,2-dihydro-2-methylisoquinoline. The observed second-order kinetics for this reaction, the rate dependence on base concentration, the absence of a spectroscopically observable intermediate, and the deuterium labeling studies (for both product structure and kinetics) are all consistent with direct hydrogen transfer from the pseudobase anion **13** to the 2-methylisoquinolinium cation. The magnitudes of the kinetic isotope effects (k_2^D/k_2^D in Table II) require C–H bond breaking in the rate-determining transition state. The small negative ρ values (eq 2 and 3) indicate a small decrease in electron density for the *N*-benzylisoquinoline derivative in the transition state relative to the reactant pseudobase anion. All of these experimental data are most readily rationalized in terms of transition state **15** which involves hydride transfer from the pseudobase anion to the 2-methylisoquinolinium cation. The ρ values of eq 2 and 3, upon comparison with ρ = −1.05 for the protonation of

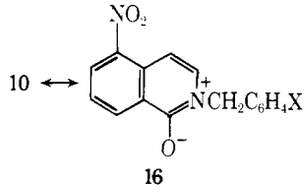


15

ring-substituted benzylamines,[18] clearly indicate that in the transition state only a small fractional positive charge is developed on the ring nitrogen atom of the *N*-benzylisoquinoline derivative; i.e., a quite "reactant-like" transition state.

The kinetic isotope effects increase with the electron-withdrawing effect of the substituent X and thus show a definite dependence on the nature of X (eq 4). This substituent dependence of k_2^H/k_2^D is the electronic reverse of that recently reported[17] for the oxidation of the same series of alkoxide ions (**13**) by ferricyanide ion. This latter reaction has $\rho(k_2^H) = -1.29$ which corresponds to a quite "product-like" transition state in contrast to the "reactant-like" transition state that is indicated for the present reaction. This dependence of substituent effect for k_2^H/k_2^D on transition state structure can be rationalized in terms of a combination of the theoretical prediction of a transition state dependent kinetic isotope effect[19] and the substituent dependence of transition state structure that is required by the Hammond postulate.[20] This argument has been presented earlier[17] for the product-like transition state in the ferricyanide oxidation of **13**, and will now be briefly enunciated for the reactant-like transition state in the present system.

A reactant-like transition state is consistent with a single-step exothermic reaction as indicated in Figure 4. As discussed previously,[17] the stability of the alkoxide ion **13** is expected to be relatively independent of the substituent X, while the stability of the isoquinolinone products **10**, represented by their zwitterionic resonance contributors **16**, will be more responsive to variations in X. Electron-withdrawing substituents (e.g., X = 4-CN) will lead to the destabilization of **16**, while electron-releasing substituents (e.g., X = 4-OCH_3) will lead to further stabilization of **16**. This situation is represented qualitatively in Figure 4. In such a case, the Hammond postulate predicts that the transition state should gradually become less reactant-like as X is varied from 4-OCH_3 to 4-CN. Theoretical treatments of primary kinetic isotope effects of asymmetric transition states predict that k^H/k^D should increase as the transition state becomes less reactant-like.[19] This prediction is in accord with the observed variation in k_2^H/k_2^D with the substituent X in the present study.



16

The substituent dependence of k_2^H/k_2^D observed in this study is particularly interesting, since the substituent effects on the kinetic isotope effect are of similar magnitudes to the substituent effects on the reaction rate (eq 2–4). In this regard, it should be noted that theoretical considerations[19] of the dependence of kinetic isotope effects on transition-state structure predict the steepest dependence of isotope effect on transition-state structure when the transition states are very reactant-like (or very product-like). Such is the case in the present reaction. There appear to be few detailed systematic experimental studies of the transition-state dependence of kinetic isotope effects. Most available experimental data in this area refer to proton transfers, usually with large isotope effects which indicate later transition states (e.g., ref 19d), and so are not directly comparable with the present data.

The products observed for this reaction are exactly analogous to the disproportionation products of heterocyclic cations in aqueous base and strongly suggest that such reactions occur via hydrogen transfer from a pseudobase alkoxide ion to a heterocyclic cation. Such a suggestion was made some years ago by Jeffs[16] but without any supporting experimental evidence. Also consistent with this mechanistic interpretation is the recent observation of Clark and Parvizi[15] that **17** and **18** react to give the products **19** and **20** at pH 10.2 much faster than the self-disproportionation of **17** and **18** individually at this pH. These workers interpret the mechanism of hydride transfer in this reaction as being via transition state **21**; however, the alkoxide ion **22** could act as hydride donor to **17** in a kinetically equivalent mechanism to **21**.

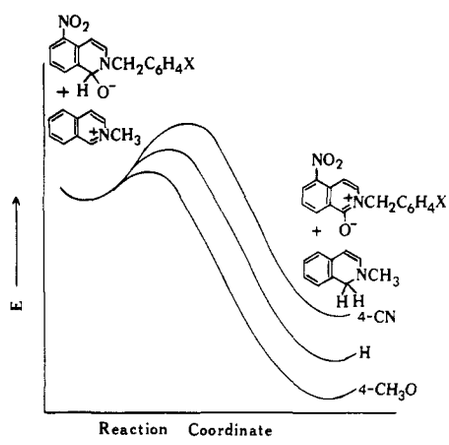
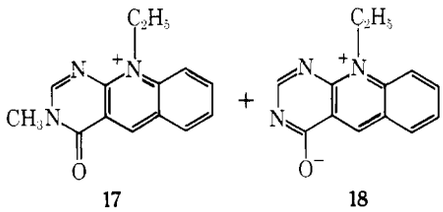
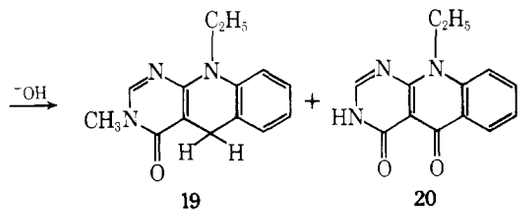
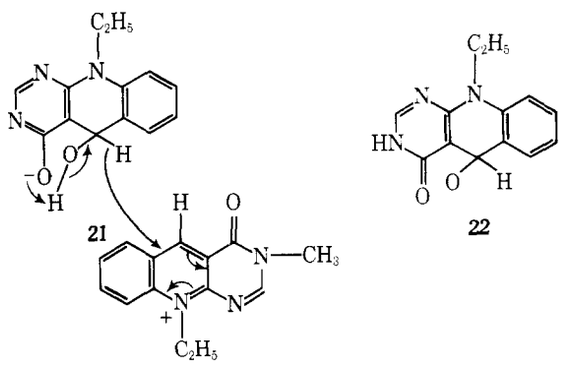


Figure 4. Schematic representation of the substituent dependence of the energy profiles for the reaction of *N*-benzyl-5-nitroisoquinolinium cations with the 2-methylisoquinolinium cation in basic solution. Curves derived as described in text and ref 17.



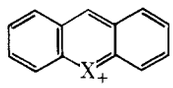




Such disproportionation via hydride transfer from pseudobase alkoxide ion to heterocyclic cation would be expected to occur most readily in those heterocyclic systems in which reasonable concentrations of cation and pseudobase anion can be obtained simultaneously. This implies ready disproportionation for those cations which have pK_{R^+} and pK_{RO^-} of similar magnitude, and particularly in those cases where $pK_{R^+} \geq pK_{RO^-}$. An example of the latter situation is the 1-methylquinolinium cation which irreversibly forms 1-methyl-2-

quinolinone in very basic aqueous solution without undergoing any spectral changes consistent with reversible pseudobase formation.[6] For this cation, pK_{R^+} has been estimated[6] as 16.5, while pK_{RO^-} may be estimated[21] as 14.4.

There are many heterocyclic pseudobases for which disproportionation has not been reported. For systems having $pK_{R^+} \ll pK_{RO^-}$, significant concentrations of heterocyclic cation and pseudobase anion cannot exist simultaneously. Thus, the rate of pseudobase disproportionation via reaction of heterocyclic cation and pseudobase anion would be quite small in such cases. However, it should also be noted that relatively ready disproportionation has been reported[12,13,22] for xanthylium and thioxanthylium cations which have extremely low pK_{R^+} values (e.g., $pK_{R^+} = -0.83$[23] for **23** (X = O) and $pK_{R^+} = -0.21$[23] for **23** (X = S)). These cations are very



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susceptible to nucleophilic attack, and apparently in these cases the neutral pseudobases are sufficiently reactive to act as hydride donors toward such very reactive cationic hydride acceptors.

Habermehl and Schunk[24] have drawn attention to the analogy between pseudobase disproportionation and the Cannizzarro reaction of aldehydes, which can be considered to be a disproportionation of the aldehyde hydrate to a carboxylic acid and alcohol. This reaction is usually considered to involve hydride transfer from either the mono- or dianion (i.e., **24** or **25**) of the aldehyde hydrate to the carbonyl group of another aldehyde molecule. The anions **24** and **25** are clearly

24 **25**

quite similar electronically to the pseudobase anion which is suggested above to be involved in hydride transfer to a heterocyclic cation in pseudobase disproportionation.

Experimental Section

Salts of the cations **8** and **14** were available from earlier studies.[17,25] 2-Methylisoquinolinium bromide was prepared by treatment of isoquinoline with methyl bromide in a Fisher pressure bottle, and the product was recrystallized several times from aqueous ethanol. Potassium chloride and acetonitrile (spectroscopic) were the best commercially available grades. Potassium hydroxide solutions were prepared by dilution of a standardized 1 M KOH solution.

Kinetic Studies. All kinetic measurements were at 25.0 ± 0.05 °C in 20% (v/v) acetonitrile–water at ionic strength 1.0 (KOH + KCl). Reactions were followed using a Unicam SP1800 spectrophotometer–Unicam AR-25 linear recorder combination at 480 nm in all cases. Concentrations of *N*-benzyl-5-nitroisoquinolinium cations were in the range $2–4 \times 10^{-5}$ M, while concentrations of 2-methylisoquinolinium bromide were in the range $0.2–1.0 \times 10^{-2}$ M. First-order plots were linear for at least 4 half-lives and rate constants were calculated from least-squares fitting of these plots.

Product Studies. A typical experiment is described. A solution (50 mL) containing 2-(4-cyanobenzyl)-5-nitroisoquinolium bromide (2.7×10^{-3} M) and 2-methylisoquinolinium bromide (4.5×10^{-3} M) in 0.1 M KOH and 40% acetonitrile was allowed to react until the pink color of the pseudobase had faded (about 2 h). Acetonitrile was removed on the rotary evaporator at room temperature, and the aqueous solution was extracted with several aliquots of chloroform. Solvent was removed from the combined chloroform extracts on the rotary evaporator at room temperature. The residue was dissolved in $CDCl_3$ and the H^1 NMR spectrum was recorded. The major peaks in this spectrum were readily assigned to a mixture of 2-(4-cyanobenzyl)-5-nitro-1-isoquinolinone[17] and 1,2-dihydro-2-methylisoquinoline.[6] Several other unidentified signals were established by control experiments to be due to decomposition products of 1,2-dihydro-2-methylisoquinoline and/or small amounts of self-reaction products of the 2-methylisoquinolinium cation. Prolonged reaction of the alkaline solution, or the use of temperature above room temperature during the workup, resulted in extensive decomposition of 1,2-dihydro-2-methylisoquinoline.

The above experiment was repeated (a) with 2-(4-cyanobenzyl)-5-nitroisoquinolinium bromide in D_2O–acetonitrile and (b) with 1-deuterio-2-(4-cyanobenzyl)-5-nitroisoquinolinium bromide in H_2O–acetonitrile. In both experiments, the relative intensities of the signals at δ 4.12 (C(1)–H) and 2.69 (CH_3) of 1,2-dihydro-2-methylisoquinoline indicated that, within experimental error, there was no incorporation of solvent hydrogen at C-1.

References and Notes

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