Kinetics and Mechanism of the Oxidation of Heteroaromatic Cations by Ferricyanide Ion[1]

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The rates of oxidation of a series of N-(X-benzyl)-5-nitroisoquinolinium cations (8) to the corresponding 1-isoquinolinones have been investigated in 20% acetonitrile–water at 25 °C, ionic strength 1.0 over the range 0.02–1.0 M KOH. These reactions are strictly first order in both heterocycle and ferricyanide and are not inhibited by up to 12-fold excess of ferrocyanide ion over ferricyanide ion. The dependence of the rate of oxidation on [OH$^-$] indicates that the rate-determining step involves ferricyanide attack on the alkoxide ion of the pseudobase derived from 8. The pH-independent second-order rate constant, k_2^H is correlated with the Hammett σ constants for the substituents X in the benzyl ring of 8: $\log k_2^H = -1.29\sigma + 2.29$. For the corresponding 1-deuterio cations the correlation line is $\log k_2^D = -0.96\sigma + 1.93$. The different ρ values for k_2^H and k_2^D indicate a kinetic isotope effect (k_2^H/k_2^D) which is dependent on the substituent X; this isotope effect varies from 1.41 for X = 4-CN to 3.25 for X = 4-CH$_3$O. The sign and magnitude of the ρ values require close to a full unit positive charge on the ring nitrogen atom in the transition state, while the magnitude of the kinetic isotope effect is only consistent with C(1)–H bond breaking in this transition state. The only mechanism consistent with both of these requirements is rate-determining abstraction of hydride by ferricyanide ion to give the isoquinolinone and a species "HFe(CN)$_6^{4-}$", which rapidly reacts with a second ferricyanide ion to give two ferrocyanide ions. The substituent-dependent isotope effect is readily rationalized in terms of a "product-like" transition state for hydride transfer. Possible structures for HFe(CN)$_6^{4-}$ are considered, and other reactions which probably also involve hydride transfer to ferricyanide are suggested.

The use of aqueous alkaline solutions of potassium ferricyanide to oxidize pyridinium ions (e.g., 1) to the corresponding pyridinones (e.g., 3) is long established as a useful
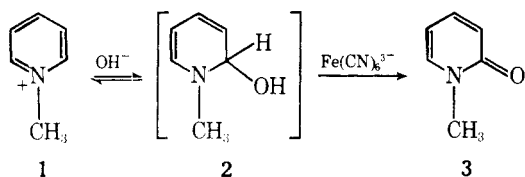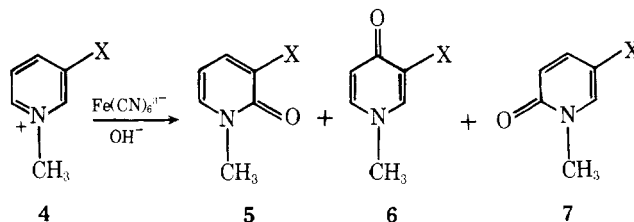

synthetic procedure.[3–11] A particularly impressive example of the use of this reaction is found in the establishment of C-4 as the site of hydride addition in the reduced form of the nicotinamide adenine dinucleotide coenzyme.[9,12] This oxidation reaction is common to all nitrogen heteroaromatic cations and has been often used for the assignment of the quaternization site in heteroaromatic molecules containing nonequivalent nitrogen atoms.[13–19]

Despite the usefulness of this reaction in synthetic and structural organic chemistry, there does not appear to have been a detailed quantitative study of the kinetics and mechanism of such ferricyanide oxidations. The reaction is generally assumed to proceed by the attack of ferricyanide ion on the pseudobase (e.g., 2) rather than by direct attack on the cation.[6,20–22] While this interpretation would appear to be quite reasonable, the first report of the influence of pH on the rate of this reaction only appeared[23] during the preparation of the current manuscript. Such a study is a minimum requirement for establishing that the pseudobase is indeed involved since the pseudobase (QOH) is involved in an acid–base equilibrium with the heteroaromatic cation (Q$^+$) as described in eq 1. For simple pyridinium ions such as 1, this equilibrium favors the cation even in very basic aqueous solutions, and no spectroscopic evidence for the presence of pseudobases in such solutions is obtainable.[24–26] However, for benzylogous pyridinium ions, or for pyridinium ions bearing strongly electron-withdrawing substituents, the presence of pseudobase species in equilibrium with the heteroaromatic cations is readily demonstrable spectroscopically, and equilibrium constants (pK_{R^+}) for eq 1 can be measured.[19,27–29]

$$Q^+ + H_2O \rightleftharpoons QOH + H^+ \qquad (1)$$
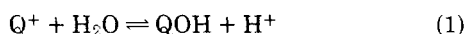
Abramovitch and Vinutha[22] have reported a semiquantitative study of substituent effects on the rates of ferricyanide oxidation of 3-substituted 1-methylpyridinium ions (4 X = H, CH$_3$, CN, CO$_2$CH$_3$). However, these substituent effects are not readily interpretable so as to provide mechanistic information on this reaction and are complicated by the presence in 4 of three nonequivalent sites that are susceptible to oxi-

dation. On the basis of the product ratio 5/7 being the same for the oxidation of the 2-deuterio and 6-deuterio isomers of 4 (X = CH$_3$), these workers concluded that cleavage of the C–H bond is not rate determining in these reactions.

We have recently reported pK_{R^+} values for the 5-nitroisoquinolinium cations (8) bearing various substituents on the benzyl ring of the N-substituent.[30] Isoquinolinium cations are
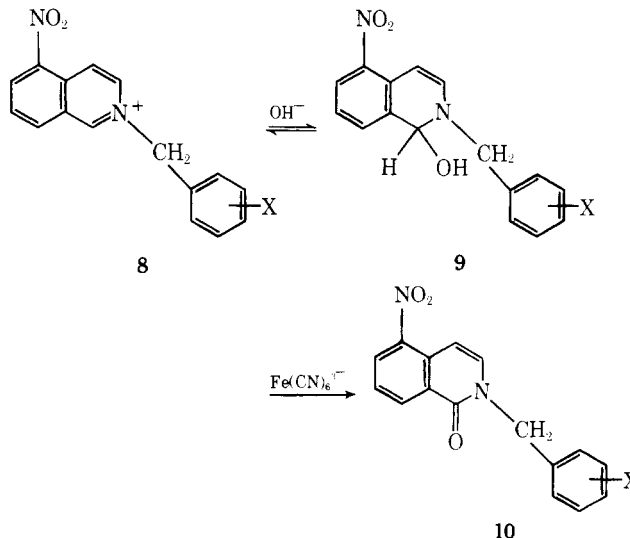
Table I. Spectral and Equilibrium Data^a for Formation of 11

X	Registry no.	λ_{max} (0.02 M KOH), nm	λ_{max} (1 M KOH), nm	K_d, M^{-1}	K_d,^{b} M^{-1}
4-CN	64840-35-3	450	493	11.9 ± 0.5	13.2 ± 1.0
3-CN	64840-36-4	452	495	9.7 ± 0.7	
4-Br	64840-37-5	456	501	11.2 ± 0.4	
3-F	64840-38-6	456	500	11.5 ± 0.6	11.3 ± 0.5
H	64840-39-7	456	504	10.2 ± 0.5	
4-CH$_3$	64840-40-0	458	506	10.1 ± 0.9	
4-CH$_3$O	64840-41-1	458	507		10.3 ± 0.9

^{a} All data in 20% acetonitrile–water at 25 °C, ionic strength 1.0 (KCl + KOH). ^{b} Data for 1-deuterio derivative.

well established[3b,31] as undergoing oxidation uniquely at C-1 of the isoquinoline moiety (e.g., **8 → 10**). We felt that a detailed kinetic study of the pH dependence and substituent effects of X on the ferricyanide oxidation of the isoquinolinium cations **8** would be useful in definitively establishing whether pseudobase species **9** are intermediates in this type of reaction. Furthermore, the substituent effect of X on the rate of oxidation has the potential for allowing a choice to be made between several alternative mechanistic pathways for these ferricyanide oxidations. Our data firmly establish that the rate-determining step in these reactions involves hydride transfer to ferricyanide ion from the alkoxide ion derived from the pseudobase. To the best of our knowledge, this study represents the first unambiguously established case of hydride ion transfer to the one-electron oxidant ferricyanide ion during the oxidation of an organic molecule.

Results

All kinetic data, spectral data, and equilibrium constants reported in this study were obtained in 20% v/v acetonitrile–water, ionic strength 1.0 (KOH + KCl) at 25 °C. In the case of **8** (X = 4-CN) additional data at 35, 45, and 55 °C were also obtained. The presence of acetonitrile in the reaction solvent was required to prevent the precipitation of the products **10** since strictly aqueous solutions tended to become cloudy during the course of the oxidation reaction even at the low concentration (7.5 × 10^{-5} M) used in this spectrophotometric study.

Solutions of each of the N-benzyl-5-nitroisoquinolinium cations (**8**) in the presence of 0.02 M KOH have a long wavelength absorption maximum in the vicinity of 455 nm (Table I). Such spectra are quite different from the spectra of these cations in neutral solution and are typical[30] of the presence of the pseudobase **9**. The pK_{R+} values for pseudobase formation from the cations **8** in aqueous solution (24.6 °C, ionic strength 0.1) vary[30] from 10.50 for **8** (X = 4-CN) to 11.62 for **8** (X = 4-CH$_3$O). The neutral pseudobase species **9** can be expected to be further stabilized relative to the cations **8** by the presence of 20% acetonitrile, so that in the present study the pseudobase should be the predominant species present in the presence of 0.02 M KOH.

In more basic solutions, the spectrum of each of the pseudobases **9** undergoes further spectral changes; a typical case is illustrated in Figure 1 for **9** (X = 4-Br). These spectral changes result in a bathochromic shift of the longest wavelength peak by 42–49 nm in 1 M KOH, as indicated in Table I. These spectral changes are readily reversible, and the presence of clean isosbestic points indicates that the pseudobases **9** are involved in a pH-dependent equilibrium with another species. The simplest rapid reversible reaction that **9** could undergo with hydroxide ion is deprotonation of the OH group to give the alkoxide ion **11**. The spectra in 0.02 M and 1 M KOH solutions also suggest formation of **11** since these spectra are consistent with relatively little electronic reorganization on equilibration in 1 M KOH solution. Equi-
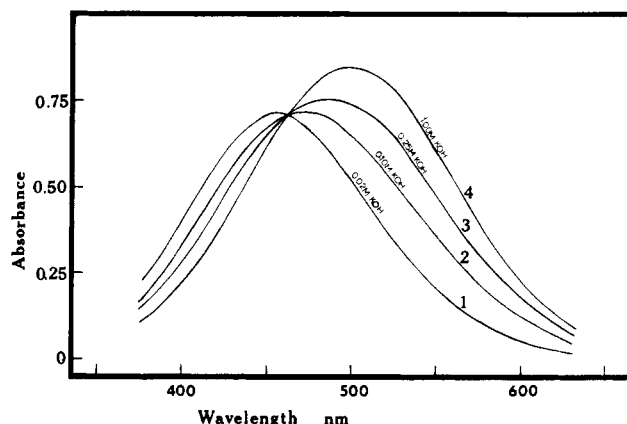

Figure 1. Spectra of **8** (X = 4-Br) in 20% CH$_3$CN/H$_2$O (ionic strength = 1.0) at various hydroxide ion concentrations: curve 1, 0.02 M KOH; 2, 0.10 M KOH; 3, 0.25 M KOH; 4, 1.0 M KOH.

librium constants, K_d = [**11**]/[OH$^-$][**9**], were calculated from the dependence of these spectra on hydroxide ion concentration and are given in Table I. The values of K_d appear to be almost independent of the substituent X in the benzyl ring. Electronic effects of X would be expected to have little influence on the equilibrium between **9** and **11** since such effects

9 **11**
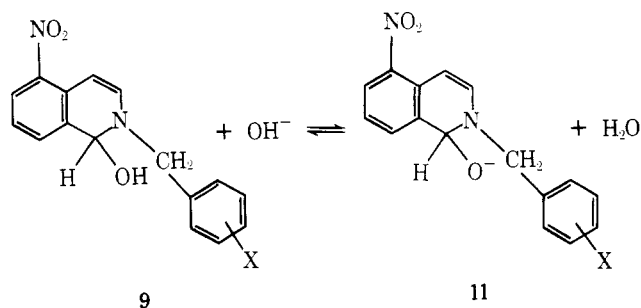
have to be transferred from the aromatic ring to oxygen through three saturated atoms.

In the presence of potassium ferricyanide, basic solutions of the cations **8** undergo spectral changes consistent with the oxidation of the heterocyclic species to the 1-isoquinolinones (**10**) and the reduction of ferricyanide to ferrocyanide. At equilibrium, the absorption spectrum of a basic solution that initially contained **8** and ferricyanide ion in a 1:2 molar ratio is identical to the spectrum of a solution of **10** and ferrocyanide ion in a 1:2 molar ratio. This is a clear indication that **10** is the only major organic product of this oxidation reaction. The time dependence of the absorption spectrum of a solution of **8** (X = H) and potassium ferricyanide in a 1:2 molar ratio in 0.02 M KOH is shown in Figure 2. The long wavelength peak that is due to **9** gradually disappears during the course of the reaction, and at equilibrium the absorbance at wavelengths greater than 450 nm is 0. Since neither ferricyanide anion,
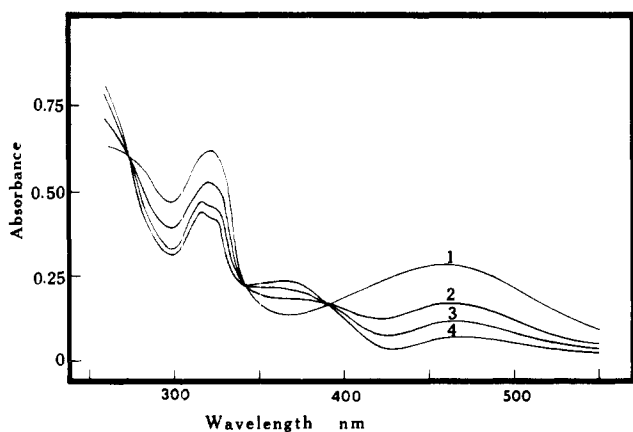
Figure 2. Time dependence of the spectrum of **8** (X = H) (7.5×10^{-5} M) and $K_3Fe(CN)_6$ (1.5×10^{-4} M) in 0.02 M KOH (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0): curve 1, 1 min; 2, 6 min; 3, 15 min; 4, 45 min.

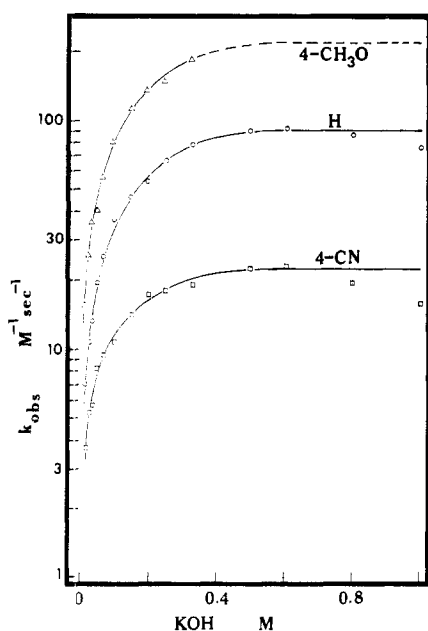**Figure 4.** Dependence of $1/k_{obsd}$ on $1/[OH^-]$ for the oxidation of **8** (X = 4-CH_3, H, 3-CN) by $K_3Fe(CN)_6$ (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0).

Figure 3. Dependence of k_{obsd} on $[OH^-]$ for the oxidation of **8** (X = 4-CH_3O, H, 4-CN) by $K_3Fe(CN)_6$ (25 °C, 20% CH_3CN/H_2O, ionic strength 1.0).

Table II. Kinetic Parameters for Oxidation of 8 and 12 by Ferricyanide Ion[a]

Cation	X	Registry no.	k_2, M^{-1} s^{-1}	K, M^{-1}
8	4-CN	64840-42-2	27.1 ± 0.7	8.0 ± 0.3
	4-CN[b]		32.4 ± 1.9	7.8 ± 0.7
	4-CN[c]		48.8 ± 4.1	9.2 ± 1.1
	4-CN[d]		71.6 ± 6.0	10.0 ± 1.2
	4-CN[e]		120 ± 6	13.1 ± 1.0
	3-CN	64840-43-3	40.4 ± 1.4	10.1 ± 0.6
	4-Br	64840-44-4	84.2 ± 8.4	7.4 ± 1.0
	3-F	64840-45-5	65.0 ± 4.5	5.8 ± 0.6
	H	52166-52-6	238 ± 80	1.7 ± 0.6
	4-CH_3	64840-46-6	262 ± 54	2.6 ± 0.6
	4-CH_3O	64840-47-7	490 ± 100	1.9 ± 0.4
12	4-CN	64840-48-8	19.2 ± 0.8	11.9 ± 0.8
	3-F	64840-49-9	42.3 ± 3.2	9.3 ± 1.0
	H	64840-50-2	84 ± 10	3.9 ± 0.6
	4-CH_3O	64840-51-3	151 ± 13	4.7 ± 0.6

[a] All data in 20% acetonitrile–water at 25 °C, ionic strength 1.0 (KCl + KOH), unless indicated otherwise; initial $[Fe(CN)_6{}^{3-}]/$ [heterocycle] = 2:1. [b] Initial $[Fe(CN)_6{}^{3-}]/$[heterocycle] = 10:1. [c] At 35 °C. [d] At 45 °C. [e] At 55 °C.

ferrocyanide anion, nor **10** shows appreciable absorption at 500 nm, the absorbance at this wavelength during the course of the oxidation reaction is a direct reflection of the concentration of unoxidized heterocycle (i.e., a mixture of **9** and **11**) at all times. Since the stoichiometry of the reaction requires the reduction of two ferricyanide ions per heterocyclic molecule oxidized, the concentration of ferricyanide at any time can also be calculated from the absorbance change at 500 nm as the reaction progresses.

All reactions studied were found to be first order in both heterocycle and ferricyanide ion (i.e., a second-order reaction overall) for at least the first 85% of the complete reaction. Observed second-order rate constants (k_{obsd}) were calculated from the slopes of second-order rate plots at at least ten different base concentrations in the range 0.02–1 M KOH. For the fastest reactions investigated, only the final 70% of the reaction was sometimes accessible, owing to the manual mixing of solutions that was used.

Values of k_{obsd} are plotted as a function of $[OH^-]$ in Figure 3 for several substituents X. In all cases a rapid increase in k_{obsd} is observed for low $[OH^-]$; k_{obsd} tends to reach a plateau at higher concentrations and then decrease slightly in the most
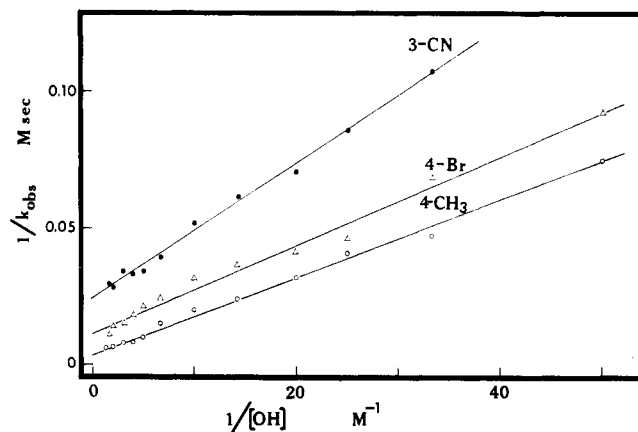
basic solutions. Plots of $1/k_{obsd}$ vs. $1/[OH^-]$ are quite linear at all $[OH^-]$ up to the maximum in k_{obsd} for each X (Figure 4). Extrapolation of these plots to $1/[OH^-]$ = 0 gives $1/k_2$, where k_2 is a second-order rate constant that is independent of $[OH^-]$. Values of k_2 evaluated in this way for each of the cations **8** at 25 °C, and also for **8** (X = 4-CN) at three further temperatures, are recorded in Table II. An Arrhenius plot based on the temperature dependence of k_2 for **8** (X = 4-CN) is quite linear and gives $\Delta H^{\ddagger}$ = 8.4 ± 0.5 kcal/mol and $\Delta S^{\ddagger}$ = −24 ± 2 eu at 25 °C.

The observed dependence of k_{obsd} on $[OH^-]$ in Figures 3 and 4 suggests that the pseudobase **9** is involved in a rapid pH-dependent equilibrium with a species Z, which then reacts with a ferricyanide ion in a rate-determining step of second-order rate constant k_2. Such a scheme leads to the rate equation

$$\frac{d(products)}{dt} = k_2[Fe(CN)_6{}^{3-}][Z]$$

$$= k_{obsd}[Fe(CN)_6{}^{3-}]([9] + [Z])$$

$$= k_{obsd}[Fe(CN)_6{}^{3-}][Z](1 + 1/K[OH^-])$$

where $K = [Z]/[9][OH^-]$. Thus, $1/k_{obsd} = 1/k_2 + 1/k_2K[OH^-]$, and K can be calculated from the slope of the linear plots in

Table III. Isotope Effects for the Oxidation of 8 and 12[a]

X	k_2^H/k_2^D	K^H/K^D
4-CN	1.41 (1.38)[b]	0.67
3-F	1.54 (1.78)	0.62
H	2.84 (2.29)	0.44
4-CH$_3$O	3.25 (2.82)	0.40

[a] Calculated from data in Table II. [b] Data in parentheses based on log $(k_2^H/k_2^D) = -0.33\sigma + 0.36$, which is derived from the correlations lines in Figure 6. This data is more reliable than k_2^H/k_2^D based on Table II since k_2^H values for X = 4-CH$_3$O and H in Table II have relatively large experimental errors.

Table IV. Influence of Added Fe(CN)$_6^{4-}$ on Oxidation of 8 (X = 4-CN)[a]

Initial [Fe(CN)$_6^{4-}$], M	Initial [Fe(CN)$_6^{3-}$], M	[Fe(CN)$_6^{4-}$]/ [Fe(CN)$_6^{3-}$]	k_{obsd}, M^{-1}s^{-1}
0	1.5 × 10^{-4}	0.0	18.6 ± 0.5
7.5 × 10^{-5}	1.5 × 10^{-4}	0.5	21.2 ± 0.2
1.5 × 10^{-4}	1.5 × 10^{-4}	1.0	22.0 ± 0.3
3.0 × 10^{-4}	1.5 × 10^{-4}	2.0	18.3 ± 0.1

[a] At 25 °C, ionic strength 1.0, in 20% acetonitrile–water; [KOH] = 0.25 M.

Figure 4. Values of K obtained in this way from the kinetic data for each cation are included in Table II.

The dependence of k_{obsd} on [OH$^-$] in the oxidation of the 1-deuterioisoquinolinium cations (**12**: X = 4-CN, 3-F, H, 4-

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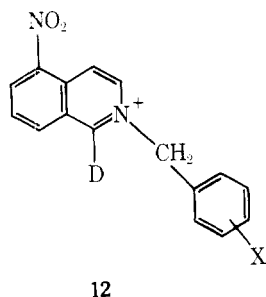
CH$_3$O) was also determined. Values of k_2, K, and K_d for these cations at 25 °C are included in Tables I and II. The isotope effects for these constants as a function of X are given in Table III.

In Figure 5, k_2 is plotted as a function of the Hammett σ constant for the substituent X for **8** and **12**. These plots are correlated by the lines from eq 2 and 3.

$$\log k_2^H = -1.29\sigma + 2.29 \quad \text{(correction coeff = 0.989)} \quad (2)$$

$$\log k_2^D = -0.96\sigma + 1.93 \quad \text{(correction coeff = 0.999)} \quad (3)$$

A study of the influence of added potassium ferrocyanide in the initial reaction solution is summarized in Table IV. It is clear that ferrocyanide ion present at concentrations up to 2-fold that of the initial ferricyanide concentration has little effect on k_{obsd}. This observation is consistent with the strict second-order kinetics that are observed over at least the first 85% of these reactions. A significant effect of the product ferrocyanide ions on these oxidations would cause marked deviations from second-order behavior.

Discussion

The observation that the kinetics of oxidation of the isoquinolinium cations **8** are first order in both heterocycle and ferricyanide ion requires a rate-determining step as indicated in Scheme I. This scheme also is consistent with the observed dependence of the rate of oxidation on hydroxide ion con-
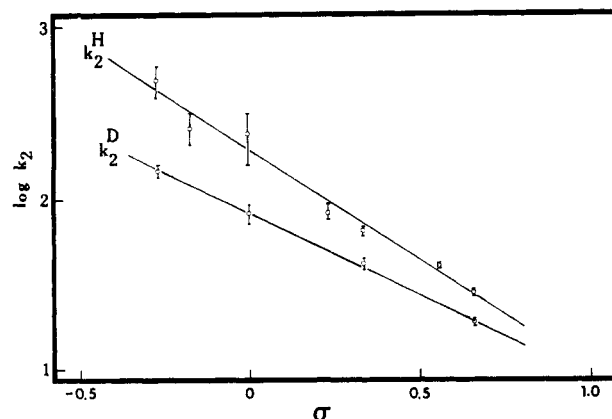

Figure 5. Hammett plots for k_2 for the oxidation of 8 and 12 by Fe(CN)$_6^{3-}$ (25 °C, 20% CH$_3$CN/H$_2$O, ionic strength 1.0).

centration and the required stoichiometry of two ferricyanide ions per heterocyclic molecule oxidized. The identification of the species Z, introduced above, as the alkoxide ion **11** is discussed further below.

Scheme I, requiring the presence of at least one intermediate, is typical of schemes which have often been proposed for a wide range of ferricyanide oxidations.[32,33] Most commonly, the intermediate has been proposed to be a radical species of some type on the assumption that since ferricyanide ion is a one-electron oxidant the rate-determining step probably involves a one-electron transfer from reductant to oxidant. A radical intermediate could then reduce a second ferricyanide ion in a second one-electron transfer step. Although there have been occasional claims[32,33] for nonradical ferricyanide oxidations, the mechanisms of such reactions have usually been written in terms of vaguely defined intermediate complexes.

Wiberg and co-workers[34] have conclusively ruled out the presence of intermediates which involve displacement of one of the cyanide ions from ferricyanide by another ligand. These workers established that for a number of ferricyanide oxidation reactions there is no incorporation of labelled free cyanide into the ferrocyanide product. This observation is also consistent with observations of the extreme difficulty in exchanging cyanide ions in ferricyanide with free cyanide from solution;[35,36] e.g., at pH 10, less than 2% of the cyanide substituents in Fe(CN)$_6^{3-}$ exchange with aqueous CN$^-$ in 100 h

Scheme I
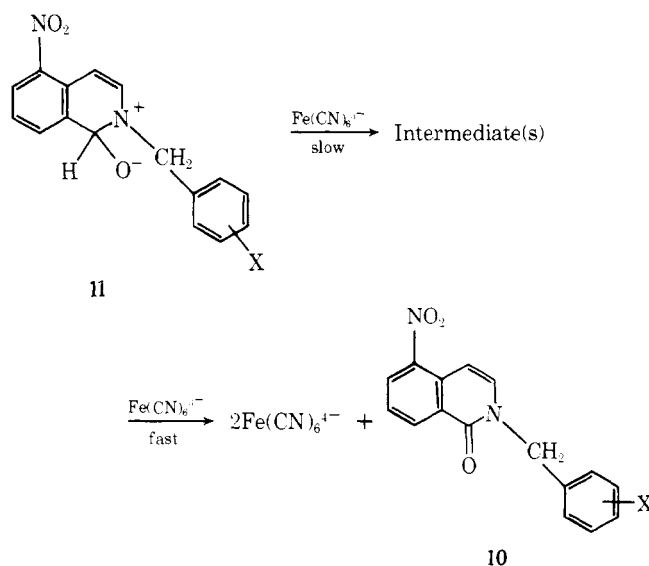
at 25 °C. Thus, a structure such as 13, which was proposed by Abramovitch and Vinutha[22] for the ferricyanide oxidation of pyridinium ions, can be ruled out for the intermediate in Scheme I.

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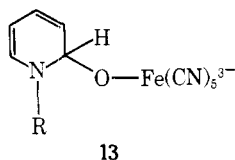
The most direct evidence in the present study which bears on the nature of the intermediate in Scheme I is contained in the observed magnitude of the ρ values for k_2^H and k_2^D. These values ($\rho(k_2^H) = -1.29$ and $\rho(k_2^D) = -0.96$) are similar to the equilibrium ρ values for protonation of ring-substituted benzylamines (14) ($\rho = -1.05$ in water at 25 °C)[37] and for the


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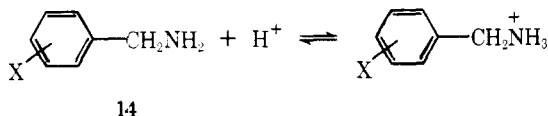
dissociation of the pseudobase 9 to the isoquinolinium ions 8 ($\rho = -1.14$ in water at 25 °C).[30] Thus, the sign and magnitude of $\rho(k_2)$ clearly indicate that the transition state for the rate-determining step in Scheme I must bear close to a full unit positive charge on the ring nitrogen atom. If the assumption is made that this transition state is quite product-like (see later discussion), then this requires that the (first) intermediate after the rate-determining transition state should also bear a positive charge on the ring nitrogen atom. Under this constraint, there would seem to be only two reasonable structures that can be proposed for the rate-determining transition state. These are (i) the transition state for the transfer of one of the lone-pair electrons on N to ferricyanide ion to generate the zwitterionic radical 15, (ii) the transition state 16 for transfer of hydride ion to ferricyanide

15   16
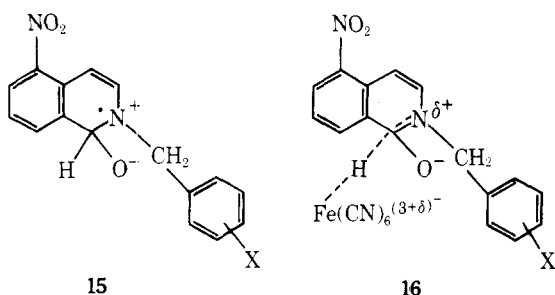
ion. For 16, $\rho(k_2^H) = -1.29$ would require the lone-pair electrons on nitrogen to be so completely involved in the transition state that the nitrogen atom would bear close to a full +1 charge in 16. Such a situation also requires a large amount of C–H bond breaking in 16.

A rate-determining transition state for electron abstraction from the anion 11 to give the oxygen radical 17, which is analogous to the radical species suggested as intermediates in the ferricyanide oxidation of phenols,[38] can certainly be ruled out on the basis of $\rho(k_2)$. Although the reaction 11 → 17

17
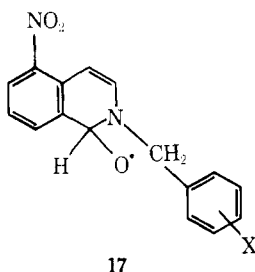
does formally involve an increase of +1 in the charge on oxygen, this process would be expected to have a very small ρ value since the oxygen atom is separated from the substituted phenyl ring by three saturated atoms (C(1)–N(2)–CH$_2$). The ρ value for 11 → 17 would be expected to be very similar to the equilibrium ρ value for 11 + H$^+$ ⇌ 9. From the data for the substituent dependence of K_d in Table I it is clear that $\rho \approx 0$ for this latter process.

Another rate-determining transition state that is formally possible for the ferricyanide oxidation of 11 is associated with hydrogen atom abstraction from C-1 to give the carbon radical 18. It is difficult to conceive of any anchimeric assistance to

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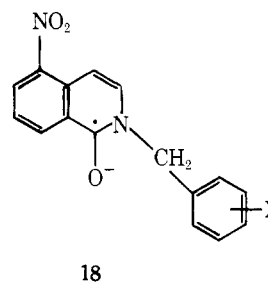
the formation of 18 from the ring nitrogen atom so as to allow the generation of close to a full unit positive charge on nitrogen. Without such assistance the ρ value for generation of 18 would be expected to be quite small since bond breaking occurs at a carbon atom that is separated from the substituent phenyl ring by two saturated atoms (N(2)–CH$_2$).

Thus, assignment of a mechanism for the ferricyanide oxidation of 11 and of a structure to the first-formed intermediate in Scheme I seems to simply require a distinction between a radical mechanism involving rate-determining formation of 15 and a hydride-abstraction mechanism via the rate-determining transition state 16. This latter mechanism, unlike the radical mechanism, involves breaking the C(1)–H bond in the rate-determining step. Thus, for transition state 16 a primary kinetic isotope effect is predicted when this hydrogen atom is replaced by deuterium, whereas for a mechanism proceeding through 15 such isotopic substitution should only lead to a very small secondary kinetic isotope effect. The values for k_2^H/k_2^D in Table III are considerably larger than can be accounted for in terms of a secondary isotope effect on the formation of 15, and so the hydride-transfer mechanism via 16 is indicated.

Of particular interest is the observation that k_2^H/k_2^D in Table III is quite dependent on the nature of the substituent X in the phenyl rings of 8 and 12. There is a smooth decrease in k_2^H/k_2^D as X becomes increasingly more electron withdrawing. This variation in k_2^H/k_2^D is over twofold between X = 4-OCH$_3$ and X = 4-CN and is so uncharacteristic of secondary kinetic isotope effects that the possibility of a radical mechanism via 15 may be confidently eliminated. The substituent dependence of k_2^H/k_2^D can, however, be readily rationalized in terms of the hydride-abstraction mechanism involving transition state 16 by reference to Figure 6. In Figure 6, it is assumed that the immediate products of the rate-determining transition state are the isoquinolinones 10 (written as the resonance contributors 19) and the species HFe(CN)$_6^{4-}$, which is the result of hydride addition to ferricyanide ion. The formal representation HFe(CN)$_6^{4-}$ is not meant to bear any implication as to the exact structure of this species (see later discussion). As pointed out above, $\rho(k_2)$ is only consistent with close to a full unit positive charge on the ring nitrogen atom in the transition state, and this in turn suggests that this transition state is quite product-like. The influence of X on the stabilities of 19 would be expected to exactly parallel the substituent effects on the transition states leading to 19. On the other hand, X will exert almost no influence on the relative

stabilities of the anions **11**, consistent with K_d (Table I) being effectively independent of X. Thus, in the reaction profiles in Figure 6 we have a situation where the stabilities of the starting materials are independent of the substituent X, but the stabilities of the products are strongly influenced by X. In such a situation the Hammond postulate[39] may be applied to predict that the transition states will vary as X is varied and be most product-like for the most unstable product (i.e., X = 4-CN in the present study).

Theoretical treatments[40] of primary kinetic isotope effects for asymmetric transition states predict that $k_2{}^H/k_2{}^D$ decreases as the transition state becomes more product-like. When viewed in this way, our data for $k_2{}^H/k_2{}^D$ as a function of X (Table III) are completely consistent with the reaction diagrams which we have derived in Figure 6 on the basis of the observed value for $\rho(k_2)$ and so further support our conclusion that the rate-determining step in these reactions involves hydride ion transfer to ferricyanide ion. It should also be noted that the $k_2{}^H/k_2{}^D$ values in Table III are similar to the primary deuterium kinetic isotope effects which have been reported for two other reactions which are generally considered to involve hydride transfer. Thus, for the Cannizzaro reaction, $k^H/k^D = 1.8$ for benzaldehyde (C_6H_5CHO vs. C_6H_5CDO),[41] while k^H/k^D is in the range 1.8–2.6 for the reduction of the triphenylmethyl cation by isopropyl alcohol [$(CH_3)_2CHOH$ vs. $(CH_3)_2CDOH$].[42]

The independence of the rate of oxidation on the presence of ferrocyanide ions up to at least a 12-fold[43] excess of ferrocyanide over ferricyanide is also atypical of those ferricyanide oxidations in which radical mechanisms have been firmly established. Ferricyanide oxidations which appear to be genuine examples of one-electron transfer processes involving radical intermediates are typically significantly inhibited by even small concentrations of ferrocyanide ions.[32,33] For example, McDonald and Hamilton[38] reported a radical oxidation of a phenol for which ferrocyanide inhibition is observed even under conditions where ferricyanide ion is in 100-fold excess over ferrocyanide ion. Such reactions show marked deviations from true first-order behavior in ferricyanide ion and are in sharp contrast to the clean overall second-order behavior observed over at least the first 85% of reaction in the current study. The deviations from second-order behavior which we do observe in this study when greater than a 12-fold excess of ferrocyanide over ferricyanide has built up are probably ascribable to specific ion effects rather than any true inhibition of the reaction by ferrocyanide ion. The rates of ferricyanide oxidations are well-known[32,33] to be susceptible to a wide range of specific ion effects from both cations and anions. The slight decreases in rate that are observed at high concentrations of KOH in Figure 4 are probably also attributable to specific ion effects arising from the replacement of chloride ion by hydroxide ion in these media. We have taken care to use only potassium salts in the current study so that cationic specific ion effects can have no influence on the interpretation of our results.

The structure of the ferricyanide hydride adduct, represented above as $HFe(CN)_6{}^{4-}$, can only be speculated upon at the present time. Clearly, this species is very unstable toward oxidation by the second ferricyanide ion that is required by the overall reaction stoichiometry. Formally, this reaction can be represented as in eq 4.

$$HFe(CN)_6{}^{4-} + Fe(CN)_6{}^{3-} \rightarrow 2Fe(CN)_6{}^{4-} + H^+ \quad (4)$$
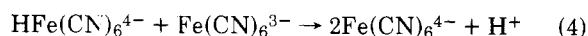
Structures for $HFe(CN)_6{}^{4-}$ can be formally written in which hydride attack has occurred at either Fe, C, or N of the $Fe(CN)_6{}^{3-}$ unit. One possibility is that this species is hexacyanohydridoiron(III), which involves a 7-coordinate Fe(III) complex. Several stable 7-coordinate Fe(III) complexes are
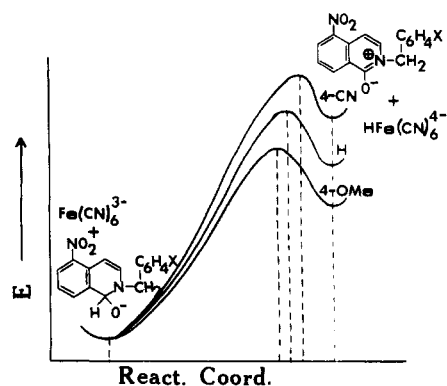

Figure 6. Energy profiles for the rate-determining step in the oxidation of isoquinolinium cations by $Fe(CN)_6{}^{3-}$. Profiles are derived as described in text.

known.[44–48] Many hydride mixed complexes of iron are known,[49] although it is not surprising that none of these are iron(III) complexes since such species are expected to be rapidly converted to iron(II) species.

An alternative attractive structure for $HFe(CN)_6{}^{4-}$ can be suggested on the basis of the recent observation by Casey and Neumann[50] that $Na^+HB(OCH_3)_3{}^-$ reacts with $Fe(CO)_5$ to give the $[Fe(CO)_4CHO]^-$ anion. This reaction involves hydride attack on the carbon atom of a coordinated CO molecule and suggests that a similar hydride attack on carbon in $Fe(CN)_6{}^{3-}$ might occur since CN^- and CO are isoelectronic. This analogy is even further strengthened by the observation[51–54] that both $BH_4{}^-$ and $HB(OCH_3)_3{}^-$ rapidly reduce $Fe(CN)_6{}^{3-}$ to $Fe(CN)_6{}^{4-}$. These reactions presumably must involve hydride attack on ferricyanide ion and may be considered to be simple models for the ferricyanide ion abstraction of hydride ion from **11** via transition state **16**. It seems likely that the same $HFe(CN)_6{}^{4-}$ species, whatever its structure, is involved in each of the above three reactions.

As discussed above, the value of $\rho(k_2)$ requires close to a full unit positive charge on the ring nitrogen atom in the transition state **16**. This requirement indicates extensive delocalization of the lone-pair electrons on nitrogen into the ring and a resulting essentially "aromatic" transition state. The requirement for a product-like transition state (see above) then suggests that a large amount of positive charge also exists on N-2 in the isoquinolinone product **10**. This requires major contributions from the Kekulé pyridinium resonance structures **19–21** to the true resonance-hybridized isoquinolinone product. The amount of aromatic character present in such isoquinolinones has been a matter of considerable dispute, and the situation has been reviewed recently.[55] The recent ex-
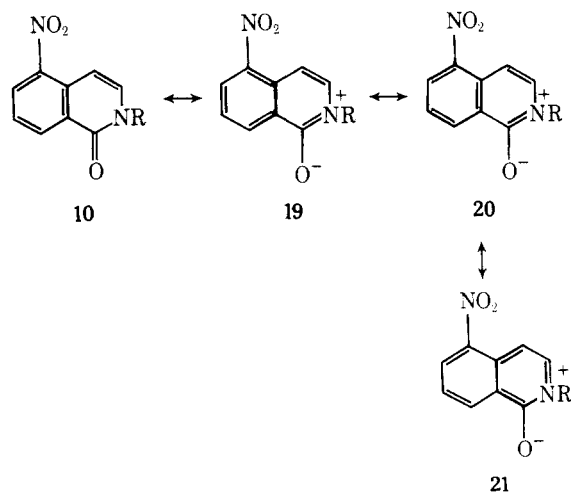
Table V. Characterization of 10 and 12

Compd	X	Registry no.	Mp, °C	^{1}H NMR,^{a} $\delta \rightarrow$	λ_{max}, nm (log ϵ)^b
10	4-CN	64840-52-4	188–189	5.30 (s, 2 H), 7.3–7.8 (m, 7 H), 8.45 (d, 1 H), 8.80 (d, 1 H)	261 (4.07), 313 (3.84), 372 (3.67)
	H	64840-53-5	155–156^c	5.22 (s, 2 H), 7.3–7.7 (m, 8 H), 8.38 (d, 1 H), 8.80 (d, 1 H)	261 (4.06), 313 (3.83), 372 (3.69)
	4-CH$_3$	64840-54-6	145–146	2.33 (s, 3 H), 5.20 (s, 2 H), 7.25 (m, 6 H), 7.53 (t, 1 H), 8.38 (d, 1 H), 8.80 (d, 1 H)	262 (4.06), 314 (3.83), 372 (3.70)
	4-CH$_3$O	64840-55-7	137–139^d (dec)	3.80 (s, 3 H), 5.16 (s, 2 H), 6.87 (d, 2 H), 7.29 (s, 2 H), 7.32 (d, 2 H), 7.55 (t, 1 H), 8.38 (d, 1 H), 8.80 (d, 1 H)	262 (4.07), 313 (3.82), 367 (3.65)
12 (Br$^-$)	4-CN	64840-56-8	260–261 (dec)	6.37 (s, 2 H), 7.7–8.1 (m, 4 H), 8.37 (t, 1 H), 8.8–9.5 (m, 4 H)	
	3-F	64840-57-9	222–224 (dec)	6.20 (s, 2 H), 7.2–7.7 (m, 4 H), 8.30 (t, 1 H), 8.7–9.5 (m, 4 H)	
	H	64840-58-0	203–204 (dec)	6.08 (s, 2 H), 7.55 (s, 5 H), 8.20 (t, 1 H), 8.7–9.4 (m, 4 H)	
	4-CH$_3$O	64840-30-8	193–194 (dec)	4.08 (s, 3 H), 6.11 (s, 2 H), 7.21 (d, 2 H), 7.65 (d, 2 H), 8.25 (t, 1 H), 8.6–9.4 (m, 4 H)	

^{a} Solvents: **10**, CDCl$_3$; **12** (Br$^-$), CF$_3$CO$_2$H. ^{b} In 20% CH$_3$CN/H$_2$O. ^{c} Anal. Calcd for C$_{16}$H$_{12}$N$_2$O$_3$: C, 68.56; H, 4.32; N, 10.20. Found: C, 68.19; H, 4.41; N, 10.34. ^{d} Anal. Calcd for C$_{17}$H$_{14}$N$_2$O$_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 66.08; H, 4.74; N, 9.33.

perimental estimate[56] of a difference of only 4.4 kcal/mol in the resonance energies of isoquinoline and 1-isoquinolinone is consistent with our conclusion of major contributions from the structures **19–21** to the resonance hybrid.

There seems to be no obvious alternative choice to the pseudobase anion **11** for the structure of the species Z introduced above on the basis of kinetic considerations. As discussed in detail above, the identification of Z as **11** allows a satisfying rationalization of the substituent effects and kinetic isotope effects observed in the present study. In particular, the formation of the 1-isoquinolinones in the rate-determining transition state via hydride abstraction from **11** is an essential feature of the rationalization via Figure 6 of the observed substituent dependence of the kinetic isotope effects. However, a comparison of the equilibrium constant for formation of **11** by deprotonation of **9** as determined by a thermodynamic method (K_d in Table I) and kinetically (K in Table II) reveals a discrepancy. Thus, the kinetically determined values of K are consistently smaller than the spectroscopically determined K_d values. Such a trend indicates that the formation of the pseudobase anion **11** from the neutral pseudobase **9** is apparently more difficult in the presence of Fe(CN)$_6{}^{3-}$ than in its absence (i.e., in the spectroscopic determination of K_d). Furthermore, there appears to be a substituent and isotope dependence on the difference between K and K_d. The overall trend is for the difference between K and K_d to become larger as the X substituent becomes less electron withdrawing, although the exact magnitude of this trend is masked by the experimental errors involved. K^D is considerably larger than K^H (Table III) and shows less deviation from K_d than K^H does for all X substituents.

The simplest rationalization for the observations of deviations between K and K_d seems to be the assumption of a rapid formation of a 1:1 complex between neutral pseudobase **9** and ferricyanide ion. The strength of this complex is required to be dependent on the substituent X and to involve some type of interaction between the C(1) hydrogen atom of **9** and ferricyanide in order to account for $K^H/K^D \approx 0.5$ (Table III). Clearly, alkoxide ion formation within a complex species of this type would be more difficult than in the neutral pseudobase because of the negative charge borne by the ferricyanide ion. We have no basis at the present time for further speculation as to the exact structure of such a 1:1 complex, but we note that there are precedents for the complexation of iron(III) species with dihydropyridine derivatives.[57-59]

In an earlier attempt at a mechanistic study of ferricyanide

oxidation of heteroaromatic cations, Abramovitch and Vinutha[22] found that the ratio of 2- to 6-pyridone product was the same for the 1,3-dimethylpyridinium cation and its C(2) and C(6) deuterated derivatives. They therefore concluded that cleavage of the C–H bond was not involved in the rate-determining step. An isotope effect of the size that we have found for **12** (X = 4-CN) ($k_2{}^H/k_2{}^D = 1.41$) could easily have been missed in this previous study since such an isotope effect could be hidden in the experimental error in the determination of the observed 3–4% of 6-pyridone in the mixture of oxidation products.[60]

In a very recent study[23] of the oxidation of pyridinium cations, Tomilenko has apparently observed the same pH dependence and first-order ferricyanide dependence for the oxidation kinetics as we report herein. However, the postulated mechanism via two consecutive one-electron transfers is not consistent with the substituent and isotope effects observed in our study.

The Cannizzaro reaction of nonenolizable aldehydes is generally considered[41,61] to involve hydride transfer from either the mono- or dianion of the aldehyde hydrate (i.e., **22** or **23**) to the carbonyl group of another aldehyde molecule. The anions **22** and **23** are clearly quite similar electronically to the
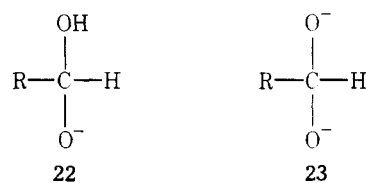
pseudobase anion **11**, which is deduced in the present study to be the species susceptible to ferricyanide attack. Thus, the current oxidation reaction may be formally considered as being analogous to the Cannizzaro reaction with hydride transfer to ferricyanide instead of to another organic molecule.

Ferricyanide ion is well-known[62,63] to oxidize aldehydes to carboxylate anions in basic solution, and so the question arises as to whether hydride transfer from **22** and/or **23** to ferricyanide ion is also involved in this reaction. Such reactions have been generally interpreted as proceeding through ferricyanide attack on the enolate anion for enolizable aldehydes. Since ketones which cannot react by hydride transfer appear to be oxidized by ferricyanide ion at similar rates to related aldehydes,[63-65] this route via the enolate ion seems to be indicated for enolizable aldehydes. However, for nonenolizable

aldehydes oxidation via hydride transfer from **22** and/or **23** seems to be the most attractive route. A detailed kinetic study of the oxidation of formaldehyde has been reported.[66] The interpretation of this reaction as passing through the radical **24** is not, however, consistent with the observed first-order

$$
\begin{array}{c}
\text{H} \\
| \\
\text{H}-\text{C}-\text{O}^{\bullet} \\
| \\
\text{OH}
\end{array}
$$

24
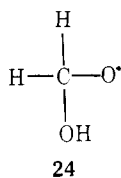
dependence on hydroxide ion concentration in the region 0.5–2.0 M NaOH. In this region formaldehyde exists essentially as its hydrated anion (**22**, R = H) since the pK_a for formation of this anion from the neutral hydrate is 13.3.[67] Thus, the observed pH dependence suggests reaction via the dianion **23** (R = H). On the basis of the current study, hydride transfer from this dianion to ferricyanide ion is clearly the most likely mechanism.

Experimental Section

Salts of the cations **8** were available from an earlier study.[30] Potassium chloride, potassium ferrocyanide, potassium ferricyanide, and acetonitrile (spectroscopic) were all the best commercially available grades.

1-Deuterio-5-nitroisoquinoline. 1-Deuterioisoquinoline was prepared from isoquinoline via 1-isoquinolinecarboxylic acid[68,69] by the method of Schleigh[70] and nitrated by the general method of Le Fèvre and Le Fèvre.[71,72] Mass spectral and ¹H NMR spectral analyses indicated >96% of the 1-deuterio derivative.

N-Benzyl-1-deuterio-5-nitroisoquinolinium bromides (12) were prepared by refluxing 1-deuterio-5-nitroisoquinoline with a slight excess of the appropriate ring-substituted benzyl bromide in acetone. The crude salts precipitated from solution and were treated with decolorizing charcoal and recrystallized from ethanol–diethyl ether. ¹H NMR spectral data and melting points are given in Table V.

Isolation of 1-Isoquinolinone Products. The bromide salt of the cation **8** (0.25 g) and a large excess of potassium ferricyanide (5 g) were dissolved in water (50 mL). Aqueous 1 M KOH (5 mL) was added dropwise with vigorous stirring until precipitation was complete. The aqueous mixture was extracted with chloroform, and the combined chloroform layers were dried over anhydrous MgSO₄. The solvent was removed on the rotary evaporator, and the residue was decolorized (charcoal) and recrystallized from methanol with addition of water to the hot solution to promote crystallization. Yields of **12** were in the range of 50–80%. Spectral and mp data are given in Table V.

Kinetic Studies. All oxidation rates were measured at 25 °C in 20% (v/v) acetonitrile–water at ionic strength 1.0 (KOH + KCl) with heterocyclic cation and ferricyanide present in the molar ratio 1:2. Typical reaction solutions (total volume 3 mL) contained heterocyclic cation (7.5×10^{-5} M), potassium ferricyanide (1.5×10^{-4} M), acetonitrile (0.6 mL), and appropriate concentrations of potassium hydroxide and potassium chloride. Appropriate modifications were made for studying the influence of ferrocyanide ion on reaction rates. Reference cells contained all components of the reaction mixture, except the heterocyclic cation. All rates were measured from recorded traces of the absorbance at 500 nm as a function of time (Unicam SP1800 spectrophotometer equipped with Unicam AR25 linear recorder). Second-order rate constants were calculated from the slopes of plots of $\frac{1}{2}(1/C - 1/C_0)$ vs. t (where C_0 is the initial concentration of heterocycle and C is the concentration at time t) using at least ten data points over the first 85% of reaction. Least-squares lines were fitted to the data points, and the computed and experimental data points were visually checked for fit and linearity.

Equilibrium constants (K_d) were evaluated from the dependence of the absorption spectrum on [OH⁻] in the range 0.02–1 M KOH (25 °C, ionic strength 1.0, 20% acetonitrile–water).

Registry No.—1-Deuterio-**11** (X = 4-CN), 64840-32-0; 1-deuterio-**11** (X = 3-F), 64840-33-1; 1-deuterio-**11** (X = 4-CH₃O), 64840-34-2; 4-cyanobenzyl bromide, 17201-43-3; 3-fluorobenzyl bromide, 456-41-7; benzyl bromide, 100-39-0; 4-methoxybenzyl bromide, 2746-25-0; 1-deuterio-5-nitroisoquinoline, 64840-31-9; Fe(CN)₆³⁻, 13408-62-3; Fe(CN)₆⁴⁻, 13408-63-4.

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Mechanism for the Reaction Involving Dimethyl Sulfoxide and Acetyl Chloride Studied by Nuclear Magnetic Resonance Spectroscopy

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The kinetics of the reaction between dimethyl sulfoxide (Me$_2$SO) and acetyl chloride (AcCl) have been studied using the nuclear magnetic resonance spectroscopy of both static and flowing liquids at 30 °C in either benzene or methylene chloride solutions. The decay of Me$_2$SO and AcCl follows mainly second-order kinetics, first order each in Me$_2$SO and AcCl. The growth of the main products, acetic acid and chloromethyl methyl sulfide, appears to be mainly second order also, although the overall reaction is complicated by several side reactions that compete to a lesser extent with the main path. These side reactions generate three previously unreported compounds in small amounts, namely, acetoxymethyl methyl sulfide, acetic anhydride, and chlorodimethylsulfonium chloride. Both the anhydride and the sulfonium salt are unstable under the reaction conditions and eventually disappear, with the salt having the faster rate. When Me$_2$SO-d_6 replaces Me$_2$SO, a primary deuterium isotope effect is observed, indicating the presence of an intermediate. This conclusion is supported by the observation that acetic anhydride and the sulfonium salt appear to be generated by trapping reactions. A mechanism to account for these observations is proposed.

Introduction

The chemistry of dimethyl sulfoxide (Me$_2$SO) has been under study for a number of years, and much is known about its nucleophilic properties.[1b] However, in the case of addition to acyl halides, conclusions concerning the reaction mechanism are based on only the nature of the products that could be identified.[2] No kinetic data seem to be available, and none of the proposed intermediates have been detected in solution at room temperature. In the present paper, we report a study of the kinetics of the reaction between Me$_2$SO and acetyl chloride (AcCl) in benzene and in methylene chloride, studied using nuclear magnetic resonance spectroscopy (NMR). In each solvent the rate of reaction appears to be second order, first order each in Me$_2$SO and ACT. The main products of this reaction are acetic acid (AcOH) and chloromethyl methyl sulfide (CMMS), as reported earlier.[2] However, small amounts of two other compounds, acetoxymethyl methyl sulfide (AMMS) and acetic anhydride (Ac$_2$O), are also generated during the reaction, and their amounts depend on the reaction conditions. In addition, a transient signal is observed in the frequency region expected for a dimethylsulfonium salt. A mechanism is proposed to account for these observations as well as the occurrence of a primary deuterium isotope effect for the disappearance of the reactants and the growth of the products.

Experimental Section

Chemicals. Me$_2$SO, Me$_2$SO-d_6, AcCl, benzene, and methylene chloride were obtained from commercial sources. Me$_2$SO and AcCl were distilled immediately before solution preparation. Benzene and methylene chloride were dried over molecular sieves, distilled, and stored over additional molecular sieves.

Kinetic Studies. The time dependence of the proton NMR spectrum was measured at 30 ± 2 °C using a Varian A-60 or HA-100-15 for the slower rates and an HA-100-15 equipped with a flow system[3] for the faster rates. Solutions of each reactant were prepared gravimetrically, and equal volumes were mixed (outside the magnet for the static runs and inside the magnet via a mixing chamber for the flow runs). Temperature regulation was not as precise as for other studies using the HA-100 flow system because the thermostated reservoir was left out to decrease solution volume.

In a complementary study, a Beckman IR-12 was used to measure the time dependence of infrared absorption bands due to Me$_2$SO-d_6 (1050 cm^{-1}) and ACT (950 and 1900 cm^{-1}) at about 25 °C after mixing equal volumes of a benzene solution containing 0.4 M Me$_2$SO-d_6 and one containing 0.4 M ACT.

Results

The CH$_3$ region of the proton NMR spectra of a nonspinning sample obtained at 100 MHz after mixing but before completion of the reaction is given in Figure 1 to illustrate the solvent dependence of the reactant and product signals. The series of spectra given for benzene solvent consists of five consecutive scans from left to right with pauses ranging from 30 s to several minutes. The first scan (labeled 1) gives CH$_3$-proton resonances for Me$_2$SO (labeled d) and AcCl (labeled a). Scan 2 illustrates an additional central signal (labeled c,h), which is a superposition of the AcOH (labeled h) and CMMS (labeled c) CH$_3$-proton resonances. The AcOH signal position as well as its intensity is time dependent moving upfield in scans 2, 3, 4, and 5, in which it is at higher field than the ACT signal. Its final position is upfield from the AcCl