2068 *J. Org. Chem.* **1986**, *51*, 2068–2071

Relative Reactivities of Heteroaromatic Cations toward Ferricyanide Ion Oxidation

John W. Bunting* and Dimitrios Stefanidis

Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada

Received April 19, 1985

The kinetics of the ferricyanide ion oxidation of the *N*-methyl cations of pyridine (also *N*-ethyl cation), quinoline, 5,6-benzoquinoline, 7,8-benzoquinoline, 1,10-phenanthroline, and phenanthridine have been investigated in 20% acetonitrile–80% water over the range pH 12–14 (25 °C, ionic strength 1.0). The initial rates of oxidation of all of these cations are first order in each of ferricyanide ion and heterocyclic cation. All cations, with the exception of the pyridinium cations, display inhibition by the ferrocyanide ion reaction product, in an analogous manner to that previously analyzed in detail for the oxidation of isoquinolinium cations (accompanying paper). The pH dependences of these oxidations are all consistent with rate-determining attack of ferricyanide ion upon the alkoxide ion of the pseudobase derived from each cation. The relative reactivities of these pseudobase alkoxide ions (of the *N*-methyl cations) toward ferricyanide ion attack are shown to be isoquinolinium > pyridinium > quinolinium ≈ 5,6-benzoquinolinium ≈ 7,8-benzoquinolinium > 1,10-phenanthrolinium > phenanthridinium > acridinium.

The base-catalyzed oxidation of heteroaromatic cations by ferricyanide ion was first reported by Decker[1] in 1891 and has often been used as a route for functionalization of an heteroaromatic ring, most commonly for nitrogen heterocycles. Despite this utility, there do not appear to be any literature reports of the relative reactivities of various nitrogen heterocyclic ring systems in such Decker oxidations. We have recently reported[2] kinetic and mechanistic studies of this reaction in a variety of isoquinolinium cation derivatives and have now extended these kinetic studies to a variety of pyridinium, quinolinium, benzoquinolinium, and phenanthrolinium cations. The relative reactivities reported herein for these oxidations should allow the prediction of the relative reactivities of a large variety of substituted derivatives of these heterocyclic cations toward this useful oxidizing agent.

Experimental Section

Bromide or chloride salts of the various heterocyclic cations were available from, or prepared as described in, an earlier study[3] from our laboratory.

All studies followed the procedures outlined in the accompanying paper[2] on the oxidation of isoquinolinium cations. The more rapid reactions were investigated in a Durrum–Gibson stopped-flow spectrophotometer, while a Cary 210 recording spectrophotometer was used for slower reactions. All kinetic data reported in this work are at 25 °C in 20% acetonitrile–80% water (v/v) at ionic strength 1.0 (KCl + KOH).

Results

1-Methylquinolinium Cation. The oxidation of the 1-methylquinolinium cation by ferricyanide ion is known to give 1-methyl-2-quinolinone[1,4] and was monitored at 420 nm under conditions in which the 1-methylquinolinium cation was present in large excess. These reactions were neither cleanly first order nor second order in ferricyanide ion concentration. Addition of ferrocyanide ion caused a large decrease in the rate of oxidation, and thus the lack of any simple kinetic order can be traced to inhibition by the ferrocyanide ion product which accumulates during the reaction. The overall kinetic observations were very similar to those reported in detail in the accompanying paper[2] for the ferricyanide ion oxidation of the 2-methylisoquinolinium cation, and we have thus again resorted to analysis of the initial reaction rates.

Pseudo-second-order rate constants (k_{2i}) evaluated from initial reaction rates are plotted as a function of pH in Figure 1. This figure also includes data for the oxidation of the 2-deuterio-1-methylquinolinium cation. Both sets of data points lie on the same line of slope 2.0. Thus these rate constants are proportional to $[^-\mathrm{OH}]^2$ and show no significant deuterium kinetic isotope effect. The dependence of initial rates upon added concentrations of ferrocyanide ion is shown in Figure 2. It is clear that $1/k_{2i}$ is linear in ferrocyanide ion concentration and that these inhibited initial rate constants do show a significant deuterium kinetic isotope effect. Similar observations were made in the study of the oxidation of isoquinolinium cations,[2] and it was shown that these data are consistent with eq 1, where $[\mathrm{Fe^{II}}]_0$ is the ferrocyanide ion concentration that is initially present.

$$k_{2i} = k_a k_b / (k_b + k_{-a}[\mathrm{Fe^{II}}]_0) \qquad (1)$$

Analysis of data such as those in Figure 2 allows the evaluation of k_a which is the pseudo-second-order rate constant in the absence of added ferrocyanide ion and the ratio k_b/k_{-a}. The pH dependence of this latter ratio is included in Figure 1 and appears to be first order in hydroxide ion concentration (unit slope). At pH 13.2, $(k_b/k_{-a})^H/(k_b/k_{-a})^D = 2.0$ which is similar to the deuterium kinetic isotope effects observed for this ratio for isoquinolinium cations.[2]

***N*-Methylbenzoquinolinium and 1,10-Phenanthrolinium Cations.** The ferricyanide ion oxidation of the *N*-methyl cations of 5,6-benzoquinoline, 7,8-benzoquinoline, and 1,10-phenanthroline are known to occur at C-2 in each case.[3] The kinetic details of each of these oxidations are very similar to those described above for the 1-methylquinolinium cation. In each case inhibition by ferrocyanide ion is observed. The pseudo-second-order rate constants based upon the initial reaction rates in the absence of added ferrocyanide ion display a pH dependence (Figure 3) indicative of a dependence upon $[^-\mathrm{OH}]^2$. Ferrocyanide ion inhibition of the initial reaction rates is consistent with eq 1, with k_b/k_{-a} being proportional to hydroxide ion concentration (Figure 3).

5-Methylphenanthridinium Cation. The general kinetic observations for the ferricyanide ion oxidation of this cation are similar to those reported above for other cations. However, this cation is unique in the current

---

[1] Decker, H. *Chem. Ber.* **1891**, *24*, 690; **1892**, *25*, 443; *J. Prakt. Chem.* **1893**, *47*, 28. Decker, H.; Kaufmann, A. *Ibid*, **1911**, *84*, 425.

[2] Bunting, J. W.; Stefanidis, D. *J. Org. Chem.*, preceding paper in this issue.

[3] Bunting, J. W.; Laderoute, K. R.; Norris, D. J. *Can. J. Biochem.* **1980**, *58*, 49.

[4] Perkin, W. H., Jr.; Robinson, R. *J. Chem. Soc.* 1913, *103*, 1973.

0022-3263/86/1951-2068$01.50/0

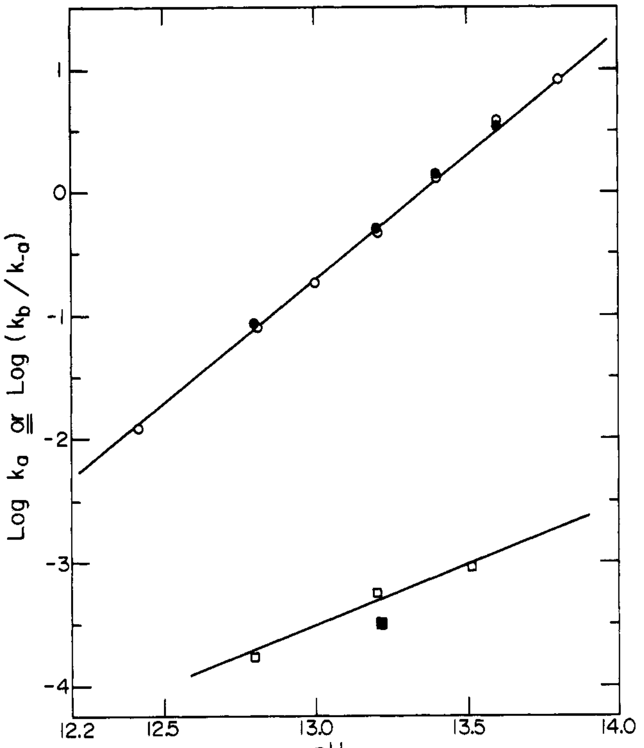


Figure 1. (a) pH dependence of log k_a (= log k_{2i}) for the ferricyanide oxidation of the 1-methylquinolinium cation (○) and its 2-deuterio derivative (●) (slope 2.0). (b) pH dependence of log (k_b/k_{-a}) for the 1-methylquinolinium cation (□) and its 2-deuterio derivative (■) (slope 1.0).

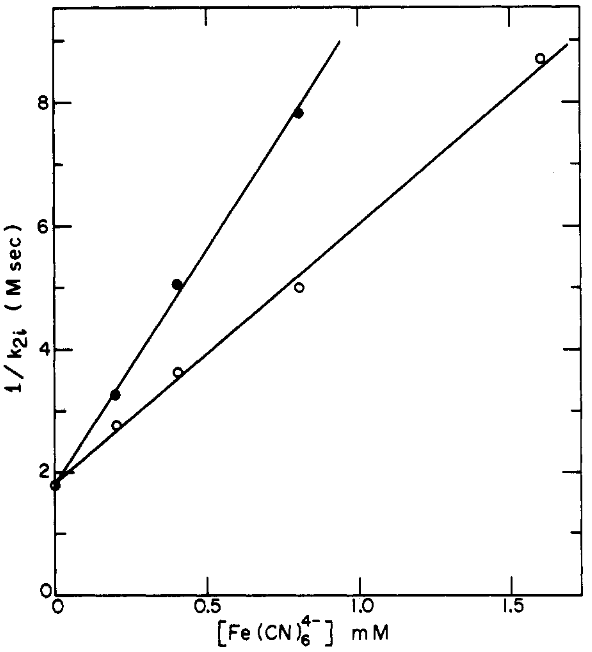


Figure 2. Dependence of second-order rate constant (from initial rates) upon ferrocyanide ion concentration for the ferricyanide ion oxidation of the 1-methylquinolinium cation (○) and its 2-deuterio derivative (●). Both sets of data at pH 13.20.

study in displaying unit slope for the log k_{2i} vs. pH plot (Figure 4) rather than a slope of 2.0 as observed for other cations. The pH dependence of k_b/k_{-a} also appears to display a weaker dependence upon hydroxide ion concentration than that found for the other cations. The least-squares slope of the log (k_b/k_{-a}) vs. pH line in Figure 4 is only 0.5 ± 0.1. Actually, the limited data available for this cation suggest an approach to a constant value for k_b/k_{-a} at high pH.

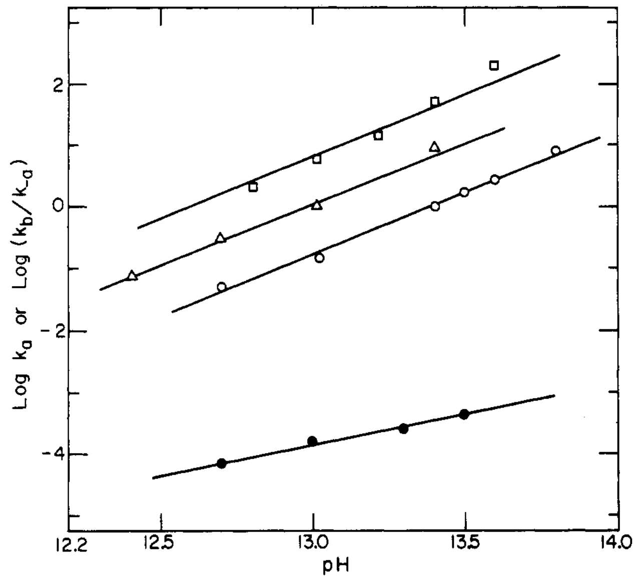


Figure 3. (a) pH dependence of log k_a (= log k_{2i}) for the ferricyanide ion oxidation of the N-methyl cations of 5,6-benzoquinoline (○), 7,8-benzoquinoline (□), and 1,10-phenanthroline (△) (lines of slope 2.0). (b) pH dependence of log (k_b/k_{-a}) for the 1-methyl-5,6-benzoquinolinium cation (●) (slope 1.0). Data points for the other two cations lie very close to this same line.

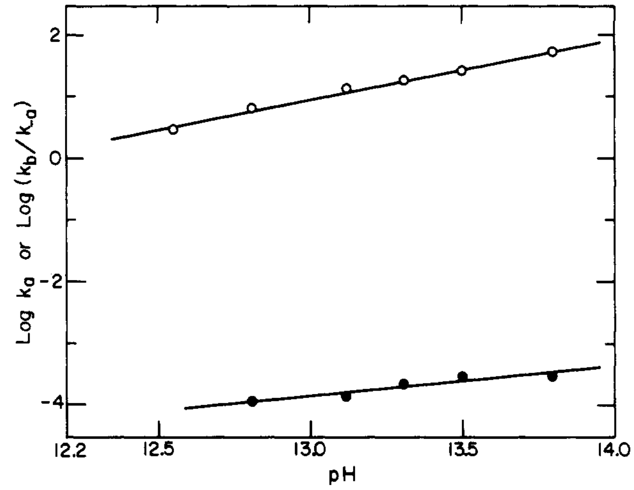


Figure 4. pH dependence of log k_a (= log k_{2i}) (○) (slope 1.0) and log (k_b/k_{-a}) (●) (slope 0.5) for the ferricyanide ion oxidation of the 5-methylphenanthridinium cation.

Pyridinium Cations. The ferricyanide ion oxidations of the 1-methyl- and 1-ethylpyridinium cations to the corresponding 2-pyridinones[5] are cleanly first order in ferricyanide ion, when these pyridinium cations are present in large excesses. Addition of ferrocyanide ion at concentrations up to 1.6 mM (i.e., >10-fold those of the initial ferricyanide ion concentration) produced no observable effect upon these pseudo-first-order rate constants. Pseudo-second-order rate constants were evaluated from the observation that the pseudo-first-order rate constants are proportional to pyridinium cation concentration. The pH dependence of these pseudo-second-order rate constants displays a dependence upon $[^{-}OH]^2$ similar to that observed for the initial rate data for quinolinium, isoquinolinium, and benzoquinolinium cations, with the N-ethyl cation being oxidized approximately half as fast as the N-methyl cation. No experimentally significant differences were observed in the rates of oxidation of the

---

[5] Prill, E. A.; McElvain, S. M. *Organic Syntheses*; Wiley: New York, 1943, Collect. Vol. 2, p 419.

Scheme I

$$Q^+ + Fe^{III} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} X + Fe^{II}$$

$$X \xrightarrow{k_b} Y$$

$$Y + Fe^{III} \xrightarrow{\text{fast}} Fe^{II} + Q{=}O$$

1-methyl-2,3,4,5,6-pentadeuteriopyridinium cation and its undeuterated analogue.

Discussion

The overall similarity of the kinetic observations in the current study and those of the previous study of the ferricyanide ion oxidation of isoquinolinium cations indicates that the mechanistic details of these oxidations are common to a wide range of heteroaromatic cations. Inhibition of these reactions by the ferrocyanide ion product has been shown[2] to be consistent with the general mechanism outlined in Scheme I, where Q^+ is the heteroaromatic cation, Q=O is its oxidation product, and Fe^{III} and Fe^{II} represent the ferricyanide and ferrocyanide ions, respectively.

This scheme predicts that the pseudo-second-order rate constants k_{2i} determined from initial reaction rates are equivalent to k_a. The observed pH dependences reported for k_a in Figures 1 and 3 are consistent with eq 2. Values for the parameter a in eq 2 are listed in Table I.

$$k_a = a[^-OH]^2 \qquad (2)$$

The only simple interpretation of this pH dependence for k_a is in terms of rate-determining ferricyanide attack upon the alkoxide ion derived from the pseudobase of Q^+. Thus the first line of Scheme I can be expanded as follows:

$$Q^+ + H_2O \overset{K_{R^+}}{\rightleftharpoons} QOH + H^+$$

$$QOH \overset{K_{RO^-}}{\rightleftharpoons} QO^- + H^+$$

$$QO^- + Fe^{III} \underset{k_{-a}}{\overset{k_-}{\rightleftharpoons}} X + Fe^{II}$$

In these terms, the pH dependence of k_a of Scheme I may be expressed as in eq 3.

$$k_a = k_-/([H^+]^2/K_{R^+}K_{RO^-} + [H^+]/K_{RO^-} + 1) \qquad (3)$$

It is known[6,7] that $pK_{R^+} > 14$ for all cations in the current study, with the exception of the 5-methylphenanthridinium cation ($pK_{R^+} = 11.94$)[8] Also pK_{RO^-} should be similar for all QOH species in the current study and is expected to be in the vicinity of 15. For $[H^+] \gg K_{R^+}$ and K_{RO^-}, which holds for all but the 5-methylphenanthridinium cation, eq 3 simplifies to

$$k_a = k_-/([H^+]^2/K_{R^+}K_{RO^-}) = k_-K_{R^+}K_{RO^-}[^-OH]^2/(K_w)^2 \qquad (4)$$

where K_w is the ionic product of water. Equation 4 corresponds to the empirically derived eq 2, with

$$k_- = a(K_w)^2/K_{R^+}K_{RO^-} \qquad (5)$$

From eq 5, the value of k_- can be calculated for each cation provided K_{R^+} and K_{RO^-} are available. Values of K_{RO^-} should be quite similar for each of the cations in Table I. We have estimated $pK_{RO^-} = 15$ from the linear free energy relationships for alcohol pK_a values.[9] Accurate pK_{R^+} values are not available for most of the cations in Table I. For the 1-methylquinolinium cation, $pK_{R^+} = 15.4$ for hydroxide addition at C-2,[10] and the pK_{R^+} value for the 1-methyl-5,6-benzoquinolinium cation is likely to be similar.[6] Indirect confirmation of this is seen in the similar a values reported for these two cations which are expected to have similar k_- values. Although resonance energies suggest[6] a similar value for pK_{R^+} for the 1-methyl-7,8-benzoquinolinium cation, the steric interaction of the N-methyl substituent with the C(10) hydrogen atom in this cation is relieved in the pseudobase, and this should lead to a reduced pK_{R^+} value, although this is known[8] to be >14. The greater a value observed for this latter cation (Table I) is probably directly attributable to this enhanced susceptibility to pseudobase formation, and thus k_- for this cation is probably not dramatically greater than for its 5,6-isomer. This steric effect is not present in the 1,10-phenanthrolinium cation, and although N(10) of this cation is expected to favor pseudobase formation, the effect is probably not very large, but does lead to a modest enhancement of a (Table I).

Table I. Rate Parameters for the Ferricyanide Ion Oxidation of Heterocyclic Cations[a]

N-methyl cation	a	pK_{R^+}	k_- ($L \cdot mol^{-1}$ s^{-1})
pyridinium	0.12	19	1.2×10^5
pyridinium[b]	0.06	19	0.6×10^5
quinolinium	21	15.4	5×10^3
isoquinolinium[c]	1.6×10^4	16.29	2×10^7
5,6-benzoquinolinium	26	15.4	7×10^3
7,8-benzoquinolinium	820	>14, < 15.4	$>8 \times 10^3$
1,10-phenanthrolinium	150	>14, <15.4	>1500
phenanthridinium	d	11.94	800
acridinium[e]		10.0	100

[a] Values of a for eq 2 in 20% CH_3CN-80% H_2O, ionic strength 1.0, 25 °C; pK_{R^+} values as discussed in text; k_- calculated from eq 5 with $pK_{RO^-} = 15$. [b] N-Ethyl cation. [c] Data from ref 2. [d] Not applicable; k_- calculated as described in text. [e] Data from ref 11.

No direct measurements of pK_{R^+} are available for the 1-methylpyridinium cation; however, from linear free energy considerations we estimate[11] this value to be >18 but <20. We have therefore used a value of $pK_{R^+} = 19$ for this cation in Table I.

The 5-methylphenanthridinium cation represents the only case in the current study for which a significant concentration of the pseudobase species exists within the experimental pH range ($pK_{R^+} = 11.94$[8]). In this case, eq 3 simplifies to

$$k_a = k_-/([H^+]/K_{RO^-}) = k_-K_{RO^-}[^-OH]/K_w \qquad (6)$$

which predicts the unit slope observed in Figure 4. From the data in this figure, $k_-K_{RO^-}/K_w = 84 \pm 4$ $L^2 \cdot mol^{-2}$ s^{-1}, and using $pK_{RO^-} = 15$, this allows the evaluation of k_- as approximately 800 $L \cdot mol^{-1}$ s^{-1}.

The most dramatic observation that is apparent upon comparison of the various k_- values in Table I is the *4000-fold greater reactivity of the isoquinolinium cation* when it is compared with the quinolinium cation. We have shown[2] that the initial electron abstraction by ferricyanide ion comes from the endocyclic nitrogen atom of the pseudobase alkoxide ion to generate a nitrogen radical cation (X of Scheme I). The quinoline pseudobase, unlike the isoquinoline derivative, is a substituted aniline, and one therefore expects delocalization of the nonbonding electrons of the nitrogen atom into the aromatic ring as

---

(6) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1.

(7) Bunting, J. W. *Heterocycles* **1980**, *14*, 2015.

(8) Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1974**, *52*, 981.

(9) Barlin, G. B.; Perrin, D. D. *Q. Rev. Chem. Soc.* **1966**, *20*, 75.

(10) Bunting, J. W.; Fitzgerald, N. P. *Can. J. Chem.* **1984**, *62*, 1301.

(11) From substituent effects upon pseudobase formation by various C-3 substituted pyridinium cations (unpublished work from our laboratory).

Table II. Ferrocyanide Ion Inhibition of the Ferricyanide Oxidation of Heterocyclic Cations at pH 13.0

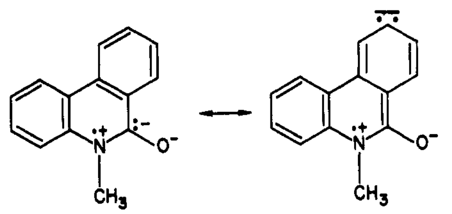
N-methyl cation	k_b/k_{-a} (mol·L^{-1})
pyridinium	*a*
quinolinium	3.5×10^{-4}
isoquinolinium[b]	5.0×10^{-5}
5,6-benzoquinolinium	1.7×10^{-4}
7,8-benzoquinolinium	9.1×10^{-5}
1,10-phenanthrolinium	1.1×10^{-4}
phenanthridinium	1.7×10^{-4}

[a] No significant ferrocyanide inhibition observed. [b] Data from ref 2.

is typical of anilines. Thus the lower reactivity of the quinoline derivative with ferricyanide ion can be traced to the reduced electron density on nitrogen in the quinoline pseudobase.

A comparison of ferrocyanide ion inhibition of the oxidation of these various cations is given in Table II in terms of the value of k_b/k_{-a} at pH 13. This ratio shows no dramatic variation amongst these cations. The relative constancy of this ratio is probably related to the fact that both k_b (base-catalyzed deprotonation of the radical species X) and k_{-a} (electron transfer to X from ferrocyanide ion) are properties of the pseudobase species and are not influenced by considerations of the aromaticities of these cations. The insensitivity of the pyridinium cation oxidations to ferrocyanide ion inhibition can probably be traced to the initial electron transfer to ferricyanide ion being rate-determining throughout the experimentally accessible pH region as a result of the extremely low concentrations of the pseudobase that are attainable in this case.

If the apparent kinetic saturation for k_b/k_{-a} at high pH in Figure 4 is real, it can probably be ascribed to an enhanced stability of the carbanionic charge in Y in this case. The C(6) hydrogen atom of X in the case of the phenanthridinium cation should be much more acidic than for any of the other cations studied since its conjugate base Y (= 1) has benzylic resonance stabilization in addition to the ylidic character common to all other Y species.



1

To date we have not investigated substituent effects upon the rates of ferricyanide oxidation of these heterocyclic cations. In the accompanying work we show that it is possible to predict the pH–rate profile for ferricyanide ion oxidation of isoquinolinium cations from the knowledge of pK_{R^+} for the cation of interest. It should be possible to establish analogous substituent effect relationships for any of the heterocyclic cations in the current study.

Acknowledgment. We appreciate the continued support of this work by the Natural Sciences and Engineering Research Council of Canada.

Registry No. *N*-Methylpyridinium, 694-56-4; *N*-ethylpyridinium, 15302-96-2; *N*-methylquinolinium, 21979-19-1; *N*-methylisoquinolinium, 33718-23-9; *N*-methyl-5,6-benzoquinolinium, 33718-26-2; *N*-methyl-7,8-benzoquinolinium, 33496-77-4; 1-methyl-1,10-phenanthrolinium, 48147-04-2; *N*-methylphenanthridinium, 33718-28-4; ferricyanide, 13408-62-3; 1-methyl-2(1*H*)-pyridinone, 694-85-9; 1-ethyl-2(1*H*)-pyridinone, 13337-79-6; 1-methyl-2(1*H*)-quinolinone, 606-43-9; 2-methyl-1-(2*H*)-isoquinolinone, 4594-71-2; 4-methyl-3(4*H*)-benzo[*f*]-quinolinone, 4594-74-5; 1-methyl-2(1*H*)-benzo[*h*]quinolinone, 4594-75-6; 1-methyl-2(1*H*)-1,10-phenanthrolinone, 31535-89-4; 5-methyl-6(5*H*)-phenanthridinone, 4594-73-4.

Glutarimidyl Chemistry: Substitution Reactions. Mechanism of "Ziegler Brominations"

U. Lüning, S. Seshadri, and P. S. Skell*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received October 10, 1985

Glutarimidyl (G·) radicals are generated in liquid-phase chain reactions by halogen atom abstractions from *N*-haloglutarimides by alkyl radicals. These reactions are carried out in the presence of small amounts of alkenes which act as halogen scavengers to eliminate halogen atom chains. The distinguishing characteristics of glutarimidyl radicals are (1) a constant hydrogen abstraction ratio, $(k_{\text{neo-C}_5\text{H}_{12}}/k_{\text{CH}_2\text{Cl}_2})_\text{H} = 5.3$ at 15 °C, over a wide range of reaction conditions, (2) no ring opening with glutarimidyls lacking 2-substituents, and (3) ring opening to make 4-bromoalkanoyl isocyanates with *N*-bromoglutarimides substituted by methyl(s) in the 2-position. Glutarimidyl radical hydrogen abstraction selectivities are characterized by early transition states for a variety of substrates, with behavior similar to that shown by chlorine atoms and by succinimidyl radicals. With adequate scavenging of bromine, using 1,3-butadiene or norbornene, brominations of benzylic hydrogen take place with the G· carrier, with selectivities similar to those obtained with Cl·, thus providing *definitive* proof that "Ziegler brominations" are not attributable to G· hydrogen abstractions.

Background

The Ziegler paper[1] describing highly selective allylic (and benzylic) brominations of alkenes with *N*-bromosuccinimide (NBS) in carbon tetrachloride medium was a landmark contribution to synthetic chemistry.[2] After recognition that this was a radical/chain substitution reaction,[3]

---

(1) Ziegler, K.; Spaeth, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Justus Liebigs Ann. Chem.* **1942**, *80*, 551.

(2) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271. Buu Hoi, N. P. *Rec. Chem. Prog.* **1952**, 13, 30. Horner, L.; Winkelmann, E. H. *Angew. Chem.* **1959**, *71*, 349

0022-3263/86/1951-2071$01.50/0 © 1986 American Chemical Society