Kinetics and Mechanism of Bromination of 2-Pyridone and Related Derivatives in Aqueous Solution

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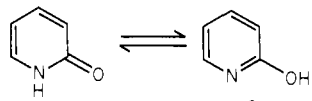
Abstract: The tautomeric system 2-pyridone ⇄ 2-hydroxypyridine (**1a** ⇄ **2a**) reacts with aqueous bromine via the principal tautomer **1a** at pH <6 and via the conjugate anion at pH >6. Attack upon **1a** occurs preferentially at the 3 position, whereas reaction upon the anion probably involves major attack at the 5 position. The facile dibromination of 2-pyridone results from the comparable reactivity of the monobromopyridones at pH <1 or pH >4. These conclusions are based upon kinetic and product studies of the bromination of **1a** and various derivatives in aqueous solutions at pH 0–8. With respect to their reactivity toward bromine the pyridones behave as substituted phenoxide ions.

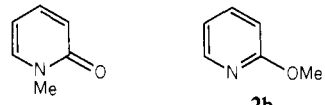
The tautomeric system 2-pyridone ⇄ 2-hydroxypyridine (**1a** ⇄ **2a**) has attracted a great deal of attention, largely because it is a prototype for the prototropic tautomerism that may be shown by many heterocyclic systems.[1] It is now known that in the gas



1a **2a**

phase and in dilute solution in nonpolar solvents the hydroxy tautomer **2a** predominates over **1a** by about 2:1.[2] On the other hand, in the strongly polar solvent water the pyridone tautomer **1a** is favored by almost 1000:1.[2]

Any given reaction of the system **1a** ⇄ **2a** may, in principle, take place upon either of the tautomers, subject to the constraints of the Curtin–Hammett principle.[2] However, without comparison to suitable model compounds it is often difficult to decide which of the two tautomers is more reactive, particularly if the reaction conditions are such as to allow their facile equilibration. The object of the present work was, in part, to ascertain what are the reactive forms involved in the bromination of **1a** ⇄ **2a** in aqueous solution. To this end we have studied this reaction and the bromination of the methyl derivatives **1b** and **2b** for comparitive purposes.



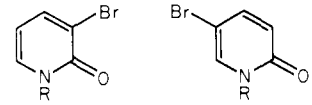
1b **2b**

The halogenation of pyridones occurs very easily, so much so that disubstitution normally results.[3] Thus 2-pyridone reacts with bromine water to produce 3,5-dibromo-2-pyridone.[3] However, both 3-bromo- and 5-bromo-2-pyridone have been detected along with the 3,5-dibromo derivative, from a bromination carried out in piperidine.[4] Heretofore the reasons for the facile dihalogenation have not been investigated. Apparently the speed of these reactions has precluded kinetic studies by conventional means.

By using the stopped-flow method we have now studied the kinetics of aqueous bromination of 2-pyridone and selected derivatives in order to clarify the main features of these reactions. The study was a natural extension of our earlier studies of the bromination of 2-pyrimidones, 4-pyrimidones, uracils, and cytosines, where different modes of reaction were uncovered.[5]

Results

In the first instance we studied the reaction of bromine with 2-pyridone (**1a** ⇄ **2a**), 1-methyl-2-pyridone (**1b**), and 2-methoxypyridine (**2b**) over the pH range 0–8. The two methyl derivatives **1b** and **2b** were chosen to serve as models of the two tautomers, **1a** and **2a**, of 2-pyridone. Due to the frequent observation of 3,5 disubstitution in the halogenation of 2-pyridone[3] it also seemed worthwhile to study the bromination of 3-bromo-2-pyridone (**3a**) and 5-bromo-2-pyridone (**4a**) and their *N*-methyl derivatives (**3b** and **4b**).



3 **4**

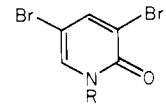
a, R = H; b, R = Me

While most of our effort has been directed toward kinetic studies over a wide range of pH, we have also carried out product studies to ascertain the circumstances under which monobromo derivatives can be obtained and particularly the position of the bromine in these products.

Product Studies. Three types of study were performed. First, reactions were conducted on a synthetic scale and the major product was isolated. Second, the course of reactions carried out in sample tubes was monitored by ^{1}H NMR. Third, the UV spectral changes accompanying bromination were recorded.

Particular attention was paid to the question of the orientation of monobromination, for which ^{1}H NMR proved most useful. For example, the isomeric bromopyridones **3** and **4** are easily distinguished, even in mixtures of the two. The 5 proton of **3** appears as a slightly broadened triplet ($J_{4,5} \simeq J_{5,6} \simeq 7.5$ Hz), whereas the 3 proton of **4** appears as a broadened doublet ($J_{3,6} \ll J_{3,4} \simeq 9$ Hz). Also, in the case of the methyl derivatives **3b** and **4b**, the *N*-methyl signals are reasonably well separated.

From the reaction of equimolar quantities of 2-pyridone (**1a**) and bromine in acetic acid an 85% yield (based on bromine) of 3,5-dibromo-2-pyridone (**5a**) was isolated. The same reaction



5a, R = H
b, R = Me

in water containing 1 equiv of KOH also produced **5a** in the same yield. However, when the medium used was 1 M aqueous KBr

(1) (a) Katritzky, A. R.; Lagowski, J. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 311. (b) *Ibid.* **1963**, *1*, 339. (c) *Ibid.* **1963**, *2*, 1. (d) *Ibid.* **1963**, *2*, 27. (e) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem. Suppl.* **1976**, *No. 1*.

(2) Beak, P. *Acc. Chem. Res.* **1976**, *10*, 186.

(3) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229.

(4) Ramirez, F., unpublished results quoted in: Meislich, H. "Pyridine and its Derivatives"; Part III; Klingsberg, E., Ed.; Wiley-Interscience: New York, 1962; Chapter 12, p 509.

(5) (a) Tee, O. S.; Paventi, M. *J. Org. Chem.* **1980**, *45*, 2072. (b) *Ibid.* **1981**, *46*, 4172. (c) Tee, O. S.; Berks, C. G. *Ibid.* **1980**, *45*, 830. (d) *Ibid.* **1982**, *47*, 1018.

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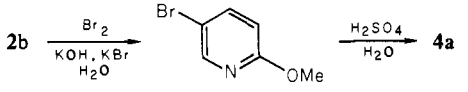
a 78% yield of 3-bromo-2-pyridone (**3a**) was obtained. This material had NMR and IR spectra identical with those of **3a** made by a literature route starting with 3-bromopyridine.[6] Furthermore, methylation of the crude product gave **3b**, identical with that prepared by other routes. A comparable bromination of **1a** was carried out in D_2O (1 M in KBr) and monitored by ^1H NMR. No significant amount of 5-bromo-2-pyridone (**4a**) was observed to be produced along with **3a**, but a small amount of **5a** precipitated out.

UV spectral studies produced similar results. At pH 3.5 equal concentrations (5×10^{-5} M) of **1a** and bromine produced a spectrum almost identical with that of **3a**. With another equivalent of bromine the 3,5-dibromo derivative **5a** was produced. At higher pH (8.1) the reaction appears to lead to **5a** more directly. However, the spectral changes accompanying the progressive addition of bromine to **1a** are consistent with the sequence **1a** → **3a** + **4a** → **5a**, although the monobromo derivatives **3a** and **4a** never dominate the spectra. By analyzing the absorbance changes at several wavelengths, using the mass balance and the extinction coefficients of **1a**, **3a**, **4a**, and **5a**, we estimate that at intermediate stages [**4a**]/[**3a**] ≃ 4.4. Since **4a** is twice as reactive as **3a** at pH 8 (vide infra), this value probably represents a lower limit for the isomer ratio **4a**:**3a** at pH 8.

A synthetic reaction of equimolar amounts of bromine and 2-methoxypyridine (**2b**) in 1 M aqueous KBr containing 0.5 equiv of KOH gave, after workup, a 63% yield of 5-bromo-2-methoxypyridine (**6**). The same product was also obtained from bromination in acetic acid containing sodium acetate, following the literature.[7] Hydrolysis of **6** in 4 M sulfuric acid gave 5-bromo-2-pyridone (**4a**), identical with that prepared by other routes.



6

Bromination of 1-methyl-2-pyridone (**1b**) in aqueous perchloric acid gave its 3,5-dibromo derivative **5b** (crystallized from solution in 67% yield) and unreacted starting material. However, the monobromo derivatives **3b** and **4b** were obtained when a buffered (pH 4) aqueous medium was used. Monitoring the reaction by NMR showed a 7:2 ratio of the 3-bromo- and 5-bromo-1-methyl-2-pyridones (**3b** and **4b**). A small amount of the 3,5-dibromo compound **5b** also precipitated from solution. UV spectral changes observed on mixing equimolar concentrations of **1b** and bromine in buffer (pH 3.5) were also consistent with the predominant formation of the 3-bromo derivative, **3b**.

As a final point we note that in none of the spectral studies (NMR or UV) did we see any evidence of intermediates of significant lifetime between the substrates and their brominated products.

Kinetic Studies. The rate of reaction of bromine with the substrates **1**, **2**, **3**, and **4** (**a** and **b**) in aqueous media with pH 0–8 was measured by the stopped-flow method.[5] In the presence of a large excess of substrate, bromine disappearance was first order and the rate constants (k_1^{obsd}) increased linearly with substrate concentration, but were unaffected by the initial bromine concentration (Tables S1–S4, supplementary material). Second-order rate constants (k_2^{obsd}) were obtained from k_1^{obsd}, taking into account the substrate concentration and the depletion of free bromine due to tribromide ion formation.[5] In some instances absorbance data were analyzed directly for second-order behavior and the values of k_2^{obsd} (corrected for tribromide formation) were invariant with both substrate and bromine concentrations. Moreover, values of k_2^{obsd} obtained from both approaches agreed well. Thus, at any given pH the reaction of bromine with the substrates studied follows a second-order rate law.

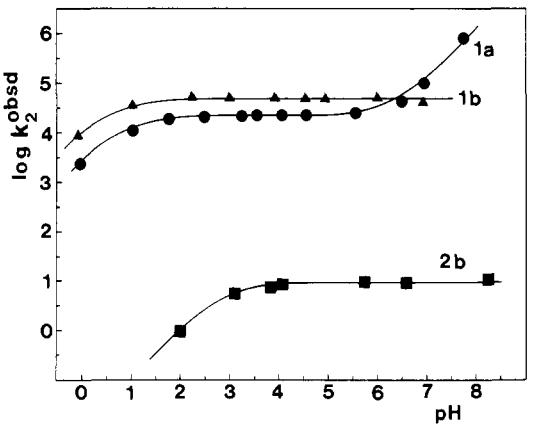


Figure 1. pH–rate profiles for the reaction of bromine with 2-pyridone (**1a**) (●), 1-methyl-2-pyridone (**1b**) (▲), and 2-methoxypyridine (**2b**) (■).

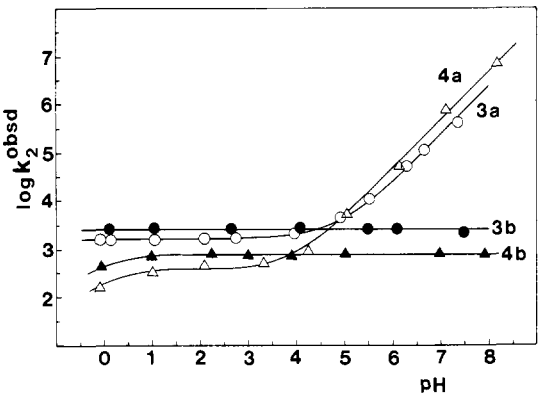


Figure 2. pH–rate profiles for the reaction of bromine with 3-bromo-2-pyridone (**3a**) (○), 3-bromo-1-methyl-2-pyridone (**3b**) (●), 5-bromo-2-pyridone (**4a**) (△), and 5-bromo-1-methyl-2-pyridone (**4b**) (▲).

Table I. Constants for the Reaction of Bromine with 2-Pyridones in Aqueous Solution[a]

substrate	pK_1	pK_2	k_2, $M^{-1}\,s^{-1}$	$k_2'K_2$, s^{-1}	k_2', $M^{-1}\,s^{-1}$
1a	0.86[b]	11.62[c]	2.2×10^4	0.012	5.0×10^9
1b	0.56[b]		4.7×10^4		
2b	2.92[b]		9.5		
3a	−2.15[c]	10.42[c]	1650	0.023	6.0×10^8
3b	−2.2[d]		2720		
4a	−0.06[c]	10.03[c]	380	0.046	4.9×10^8
4b	−0.1[d]		760		

[a] Parameters used to generate profiles in Figures 1 and 2 with eq 1, 2, or 3. [b] By fitting. [c] Taken from ref 7 and 8. [d] Assumed.

The variations of k_2^{obsd} with pH for 2-pyridine (**1a** ⇌ **2a**), 1-methyl-2-pyridone (**1b**), and 2-methoxypyridine (**2b**) are depicted in Figure 1. Since the literature protonation p*K*s for **1b** and **2b** are 0.32[8] and 3.28,[7] respectively, the pH–rate profiles for these substrates suggest that they simply react as their free-base forms. Thus the acidity dependence of k_2^{obsd} for **1b** and **2b** can be described by eq 1, in which k_2 is the second-order rate constant for attack of bromine upon the free-base form of the substrate, and K_1 is the acid dissociation constant of its conjugate acid. The curves in Figure 1 drawn through the data points for **1b** and **2b** were calculated with eq 1 and the parameters given in Table I.

$$k_2^{obsd} = k_2K_1/(K_1 + [H^+]) \quad (1)$$

Similar pH behavior is exhibited by 3-bromo-1-methyl-2-pyridone (**3b**) and by 5-bromo-1-methyl-2-pyridone (**4b**) except that little or no curvature is evident in the data (Figure 2) since

(6) (a) Matsumara, E.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3144. (b) Cava, M. P.; Weinstein, B. *J. Org. Chem.* **1958**, *23*, 1616.
(7) Spinner, E.; White, J. C. B. *J. Chem. Soc. B* **1966**, 991, 996.
(8) Albert, A.; Phillips, J. N. *J. Chem. Soc.* **1956**, 1294.

they have protonation pKs <0.[7] Therefore for virtually all of the pH range studied $K_1 \gg [H^+]$ so that eq 1 becomes $k_2^{obsd} = k_2$, and the rate constants for **3b** and **4b** are invariant in the pH range 0–8.

For 2-pyridone ⇄ 2-hydroxypyridine (**1a** ⇄ **2a**) the pH–rate profile (Figure 1) suggests reaction upon the free base **1a** (or **2a**) up to pH 6. Above this the rate increases, suggesting reaction upon the anion of the substrate. An additional term must be added to eq 1 to take into account this behavior at higher pH, as shown in eq 2. The calculated curve for **1a** shown in Figure 1 was generated from eq 2, which is appropriate for reaction upon the

$$k_2^{obsd} = \frac{k_2K_1}{(K_1 + [H^+])} + \frac{k_2'K_2}{[H^+]} \qquad (2)$$

free-base form and upon the anion at pH $\ll$ pK_2 (=11.62),[8] the pK for anion formation. In eq 2 k_2 and K_1 have the same meaning as in eq 1, k_2' is the rate constant for bromine attack upon the anion, and K_2 is the acid dissociation constant of the substrate forming the anion. The values used for calculation of the curve for **1a** are given in Table I.

The pH–rate profiles for 3-bromo-2-pyridone (**3a**) and 5-bromo-2-pyridone (**4a**) (Figure 2) may also be described by eq 2. However, since the protonation pKs of **3a** and **4a** are <0,[7] for most of the pH range studied the condition $K_1 \gg [H^+]$ applies and so eq 2 can be simplified to eq 3. This equation adequately describes the behavior of **3a** and **4a** over the range of pH 0–8 when when the values of k_2, k_2', and pK_2 given in Table I are used.

$$k_2^{obsd} = k_2 + k_2'K_2/[H^+] \qquad (3)$$

In summary, the reaction of bromine with all of the substrates follows a second-order rate law at fixed pH. Second-order rate constants vary with pH in a manner consistent with reaction upon the free-base form of the substrate, but the pyridones bearing ionizable hydrogens (**1a**, **3a**, **4a**) also react via their anions at higher pH.

Discussion

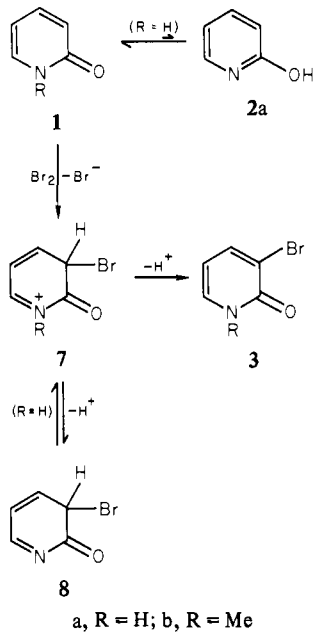
Reactive Forms. As is clearly seen in Figure 1 and from the relevant values of k_2 in Table I, the tautomeric system **1a** ⇄ **2a** shows a reactivity toward bromine which is very similar to that shown by 1-methyl-2-pyridone (**1b**), but much greater (2300×) than that shown by 2-methoxypyridine (**2b**). Since the pyridone tautomer **1a** predominates in aqueous solution,[2] this observation is compelling evidence that 2-pyridone (**1a**) reacts as such and not via its hydroxy tautomer **2a** at pH <6. As pointed out earlier, reaction upon the anion of 2-pyridone apparently takes over at pH >6.

The situation with the bromopyridones **3a** and **4a** is comparable. At pH <4 they show very similar reactivities to their respective *N*-methyl derivatives (**3b** and **4b**), suggesting that reaction upon their hydroxy tautomers is unimportant in aqueous bromination. Again, at higher pH reaction takes place upon the anions of **3a** and **4a** (see Figure 2).

The positional selectivities observed for **1a**, **1b**, and **2b** also show significant differences. Bromination of 1-methyl-2-pyridone (**1b**) occurs mainly at the 3 position, whereas 2-methoxypyridine (**2b**) reacts at the 5 position. The tautomeric system **1a** ⇄ **2a** reacts to yield the 3-bromo product **3a**, providing further evidence that the reactive form is the pyridone tautomer **1a**. In contrast, at higher pH where 2-pyridone reacts via its anion, UV spectral studies suggest that attack at the 5 position of this anion predominates. This behavior is reminiscent of phenols and phenoxide ions which show greater para than ortho reactivity.[9]

Katritzky and co-workers[10] studied the nitration of 2-pyridones in strong acid and their hydrogen isotope exchange in deuterated acid at elevated temperatures. For these reactions they also concluded that the reacting species was the free-base form of tautomer **1a**.[10]

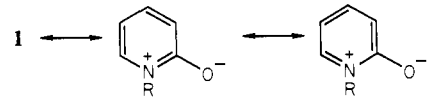
Scheme I



1 2a 7 3 8

a, R = H; b, R = Me

Reactivities. The comparison to phenoxides, alluded to above, may be extended further. Acheson[11] stresses the contributions to the structure of 2-pyridones from the dipolar valence-bond forms **1'** and **1''**. These contributions can account for various properties



1' 1''

of 2-pyridones,[11] including the predominance of the tautomer **1a** over **2a** in aqueous solution.[2] Seen in this light 2-pyridone may be considered as a phenoxide ion bearing an ortho azonium nitrogen (=$^+$NH–),[12] and Katritzky et al. have employed this type of approach in discussing reactivities of 2- and 4-pyridone in hydrogen-exchange reactions at elevated temperatures.[10b] The anion of 2-pyridone, of course, is a phenoxide ion with an ortho aza nitrogen (=N–) substituent.[12] Thus, from the present rate data we can estimate a value of ρ^+ for the bromination of phenoxides.

Using $\sigma_m^+ = 0.54$ for aza nitrogen,[12] a value of 2.00 for azonium nitrogen,[12,13] and the appropriate rate constants for **1a** and its anion (Table I), we calculate $\rho^+ = -3.67$. Likewise from the reactivities of **3a** and **4a** and their respective anions we calculate values of −3.81 and −4.19. These values are more negative than the approximate value of −3.5 estimated by Kulic and Vecera.[14] Their estimate, however, is based on data covering a small range of reactivity (1 power of 10) near the diffusion-controlled limit,[15] whereas the present values derive from data covering seven powers of 10. If one uses the data for *p*-bromophenoxide ($k_2' = 7.8 \times 10^9$ M^{-1} s^{-1}) and 2,4-dinitrophenoxide ($k_2' = 1.0 \times 10^6$ M^{-1} s^{-1}) from Bell and Rawlinson,[9] one calculates $\rho^+ = -4.19$.[16] Taken overall we believe these values support the notion that the 2-pyridones studied here are behaving as substituted phenoxide ions.

(9) (a) Bell, R. P.; Rawlinson, D. J. *J. Chem. Soc.* **1961**, 63. (b) Tee, O. S.; Paventi, M., unpublished work.

(10) (a) Brignell, P. J.; Katritzky, A. R.; Tarhan, H. O. *J. Chem. Soc. B* **1968**, 1477. (b) Bellingham, P.; Johnson, C. D.; Katritzky, A. R. *Ibid.* **1967**, 1226; **1968**, 866.

(11) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds"; 2nd ed.; Interscience: New York, 1967; Chapter 5.

(12) Tomasik, P.; Johnson, C. D. *Adv. Heterocycl. Chem.* **1976**, *20*, 1.

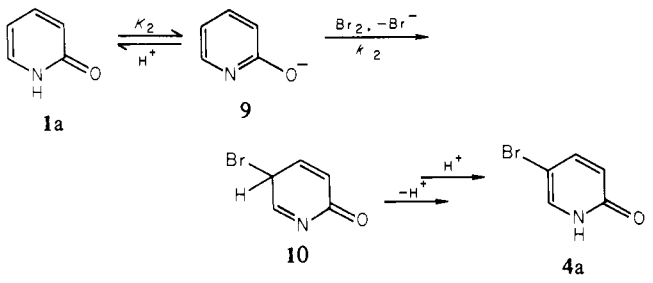
(13) Estimated values of σ_m^+ for =$^+$NH– span the range 1.85–2.18.[10,12] We have taken 2.00 as an average value.

(14) Kulic, J.; Vecera, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 71.

(15) Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

(16) (a) Using $\sigma_m^+ = 0.41$ and 0.67 for Br and NO_2, respectively.[16b] (b) March, J. "Advanced Organic Chemistry"; McGraw-Hill: New York, 1968; p 241.

Scheme II



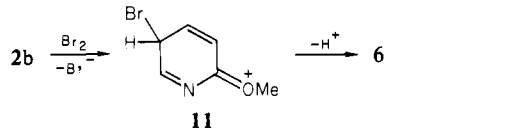
The reactivity shown by 2-methoxypyridine (**2b**) toward bromine is appropriate for an aza-substituted anisole. For anisole itself $k_2^{obsd} = 5.5 \times 10^4$ M^{-1} s^{-1}, and $\rho^+ = -7.0$ for substituted anisoles.[17] From these values and taking $\sigma_m^+ = 0.54$ for aza nitrogen,[12] we calculate $k_2 = 9.1$ M^{-1} s^{-1} for **2b**, in excellent agreement with the observed value of 9.5 M^{-1} s^{-1}. This concordance is strong evidence against any special interaction between bromine and the ring nitrogen of **2b**, or any significant formation of a complex Br_2:**2b** prior to reaction.[18]

Mechanism. The simplest mechanism of bromination consistent with the data for **1a** and **1b** is that shown in Scheme I. It involves preferential attack of bromine at the 3 position of the pyridone **1** followed by deprotonation of the cation **7** to yield the monobromo product **3**. As remarked above we found no spectral evidence for the buildup of any relatively long-lived intermediates.[19] The azacyclohexadienone **8** may well be involved in bromination of **1a**, even though its concentration is never high enough[21] (for long enough) to be observed. All things considered, we feel that the mechanism shown in Scheme I best represents the reaction of bromine with **1b** and with **1a** (for pH <6).

At higher pH 2-pyridone (**1a**) appears to react with bromine via its anion **9**, principally at the 5 position (Scheme II). By analogy with phenoxide, this probably involves formation of the azacyclohexadienone **10** which rapidly tautomerizes[21] to the monobromo derivative **4a**.

The kinetic data for the 3-bromo- and 5-bromo-2-pyridones (**3** and **4**) are similar to those for **1a** and **1b** though modified by lower reactivities and different pK values. Presumably, therefore, these compounds react with bromine by mechanisms analogous to those depicted in Schemes I and II.

Bromination of 2-methoxypyridine (**2b**) proceeds at a rate appropriate to an aza-substituted anisole (vide supra) and leads to the formation of the 5-bromo derivative **6**. Accordingly the



reaction most likely involves bromine attack at the 5 position followed by relatively fast deprotonation of the cation **11**, by analogy with anisoles.[17]

Disubstitution. The present work sheds considerable light on the frequent observation of dihalogenation of 2-pyridone (**1a**).[3] Apparently it results because there is a relatively short range of pH (1–4) in which **1a** is appreciably more reactive toward bromine than either of its monobromo derivatives **3a** or **4a**. At pH >5, reaction via the anions of **3a** and **4a** becomes equal to or faster than reaction upon the anion of **1a** (cf. values of k_2'/K_2 in Table I). This arises because the higher reactivity of the anion **11** is more than offset by the larger values of K_2 for **3a** and **4a** (Table I).

In acid solution, where protonation of **1a** becomes significant, a similar situation develops. Here the difference in reactivity of **1a** and **3a** (factor of 13) is offset by the difference in their values of K_1 (factor of 1000, Table I). The same applies to the methyl derivatives **1b** and **3b**, so that observation of dibromination of **1b** in acid solution is understandable.

It should be noted, however, that even in the pH range 1–4 the ratio of reactivities **1a**:**3a** is not large at 13:1. Thus, after 93% reaction **3a** can compete with **1a** for bromine, and a small amount of the 3,5-dibromo derivative **5a** can be formed. Again, a similar situation applies to the methyl derivatives **1b** and **3b**, where the ratio of reactivities is only 17:1 (Table I). Thus our observation of the formation of small amounts of the 3,5-dibromo products **5** from brominations of **1** carried out in buffered media (pH 4) in NMR tubes is explicable.

Experimental Section

Kinetic Methods. The stopped-flow apparatus, data acquisition, and data analysis were as in other recent work.[5] All kinetics solutions were 1.0 M in potassium bromide and except for the highest acidities $\mu = 1.0$ M. For pHs >1 a "universal" buffer ($CH_3COOH/H_3PO_4/H_3BO_3$/NaOH),[22] total concentration 0.01 M, was used. Reactions were followed by monitoring bromine disappearance at 255–300 nm (tribromide ion band) with the stopped-flow observation cell thermostated at 25.0 ± 0.1 °C. Second-order rate constants were corrected for the formation of tribromide ion and hypobromous acid.[5c] The dissociation constant of the tribromide ion was taken to be 0.0625 M (for $\mu = 1.0$ M (KBr)).[23]

Spectral Studies. UV studies were carried out in the same media as for the kinetic studies (vide supra). Spectra were obtained on an Aminco DW-2 UV–vis spectrophotometer. ^1H NMR spectra were measured on Varian T-60 and A-60 instruments. For both UV and ^1H NMR studies two types of experiments were conducted: (a) the mixing of equimolar amounts of substrate and bromine; (b) the incremental addition of bromine up to, and sometimes above, the amount of substrate present.

Substrates and Products. The compounds employed in this work are all known from the literature. Below we simply detail procedures which deviated from the literature and which were germane to the reactions studied. The position of bromine in monobromo derivatives was checked by NMR and by conversion to other derivatives.

UV and IR spectral data for the compounds studied may be found in the literature.[7,8]

2-Pyridone (1a) (Aldrich) was recrystallized three times from petroleum ether to give long needles, mp 106–107 °C (lit.[10b] mp 106 °C, after sublimation). Its **sodium salt** separated as plates upon addition of acetone to an ethanolic solution of equimolar amounts of **1a** and sodium ethoxide. Several recrystallizations from ethanol gave a hydrate,[24] mp 165–167 °C. ^1H NMR indicated ~2 waters of crystallization, as did titration with standardized acid. Elemental analysis was not particularly good. Anal. Calcd for $C_5H_4NONa \cdot 2H_2O$: C, 39.22; H, 5.27; N, 9.14. Found: C, 40.59; H, 4.43; N, 8.90. However, kinetic runs with recrystallized **1a** and the sodium salt (assumed to be the dihydrate) gave identical second-order rate constants (Table S1, supplementary material).

1-Methyl-2-pyridone (1b) (Aldrich) for use in kinetic experiments was converted to its **hydrobromide salt**: **1b** was reacted with a slight excess of concentrated HBr in acetone. The solution was evaporated and the residue was recrystallized from acetone. After being dried at 110 °C, the crystals had mp 174–177 °C (lit.[26] mp 175–176 °C). ^1H NMR and IR spectra agreed with those in the literature.[26]

2-Methoxypyridine (2b) (Aldrich) was used as received. Attempts to use its HBr salt (prepared as above) were unsuccessful since this salt undergoes hydrolysis to **1a** upon standing in aqueous solution.

3-Bromo-2-pyridone (3a) was prepared from 3-bromopyridine by N-oxidation[6a] and rearrangement.[6b]

3-Bromo-1-methyl-2-pyridone (3b). To **3a** (0.45 g, 2.59 mmol) in 50 mL of methanol was added an equivalent amount of NaOMe in 5 mL of MeOH. After the solution was stirred for 5 min, dimethyl sulfate (0.65 g, 5.2 mmol) was added and the mixture was warmed at 50–60 °C for 3 h. The resultant solution was made basic with NaOMe (pH 8–9, test paper), and 60 mL of 1:1 acetone/chloroform was added to complete precipitation of salts. The remaining solution was filtered and reduced

(17) Aaron, J. J.; Dubois, J. E. *Bull. Soc. Chim. Fr.* **1971**, 603.
(18) We specifically raise this point because 4-methoxypyridine forms a relatively stable 1:1 complex with bromine which retards its bromination.[9b]
(19) We have observed adduct formation for various pyrimidone derivatives.[5d,20]
(20) (a) Tee, O. S.; Banerjee, S. *Can. J. Chem.* **1974**, *52*, 451. (b) *J. Org. Chem.* **1979**, *44*, 3256. (c) *Can. J. Chem.* **1979**, *57*, 626.
(21) In the bromination of simple phenols and phenoxides in aqueous solution bromine decrease and product increase proceed at the same rate.[14] Since cyclohexadienone buildup is unimportant in those cases, it is unlikely to be important here.
(22) Coch Fugoni, J. A. *Gazz. Chim. Ital.* **1957**, *87*, 403.
(23) Jones, G.; Baeckstrom, S. *J. Am. Chem. Soc.* **1934**, *56*, 1517.
(24) Problems of hydration were encountered by Spinner, who gave no melting point for this hydrated sodium salt.[7,25]
(25) Spinner, E. *J. Chem. Soc.* **1960**, 1232.
(26) Cook, D. *Can. J. Chem.* **1965**, *43*, 749.

to an oil which was dissolved in benzene, filtered again, and evaporated to give a slightly yellow oil (0.41 g, 85%), characterized by NMR and IR. The material used for kinetics runs was distilled, bp 117-120 °C (0.1 mm Hg) (lit.[27] bp 120-125 °C (0.5 mm)).

5-Bromo-2-pyridone (4a) was prepared as outlined in the literature.[28] For reasons of solubility the **sodium salt** was used for kinetic experiments. It was prepared as follows: In a minimum amount of water **4a** was dissolved with an equivalent amount of NaOH. The solution was filtered, and acetone was added to the filtrate to precipitate the sodium salt which was filtered off and washed with acetonitrile. Recrystallization from 2 parts EtOH/5 parts CH_3CN gave a product with mp 349-350 °C dec. ^1H NMR showed this to be dihydrate, as did analysis. Anal. Calcd for $C_4H_3BrNONa\cdot 2H_2O$: C, 25.89; H, 3.02; N, 6.04; Br, 34.45. Found: C, 26.21; H, 3.07; N, 6.30; Br, 34.29.

5-Bromo-1-methyl-2-pyridone (4b). To an ethanolic solution of the sodium salt of **4a** was added a slight excess of methyl iodide. The solution was refluxed for 10 min and evaporated to dryness. Recrystallization of the residue from benzene-ligroin gave slender white needles (60% yield), mp 65-67 °C (lit.[27] mp 62-63 °C), with appropriate spectra.

5-Bromo-2-methoxypyridine (6) was prepared by bromination of **2b** in acetic acid[7] and as follows: To **2b** (1.1 g, 10 mmol) and KOH (0.28 g, 5 mmol)[29] in 60 mL of water was added bromine (1.6 g, 10 mmol) in 60 mL of 1 M aqueous KBr. The solution was stirred for 3.5 h until the bromine color disappeared. The solution was made basic and extracted with 2 × 100 mL of $CHCl_3$. The extract was dried (Na_2SO_4) and reduced to an oil (1.1 g, 63%). ^1H NMR showed **6** with a trace of the starting material, **2b**.

The position of the bromine was confirmed by hydrolysis: The above oil was refluxed in 4 M sulfuric acid for 2.5 h. The cooled solution was brought to pH 4 and evaporated to dryness. The solid was extracted with benzene and evaporation of the solvent gave **4a**, identical (NMR, IR, mp) with that prepared as above.

(27) Bradlow, L.; Vanderwerf, C. A. *J. Org. Chem.* **1951**, *16*, 73.
(28) Fox, B. A.; Threlfall, T. L. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 346. Seide, O. *Chem. Ber.* **1924**, *57*, 1802.
(29) Since **2b** (and probably **6**) can be hydrolyzed in aqueous acid.

Bromination of 2-Pyridone (1a). (a) In Acetic Acid. To **1a** (1.9 g, 20 mmol) in 10 mL of acetic acid was slowly added bromine (3.2 g, 20 mmol) in 40 mL of acetic acid. When this solution was reduced to one fifth of its volume crystals of 3,5-dibromo-2-pyridone (**5a**) were deposited. Recrystallization gave **5a** (85% yield) with an IR spectrum as reported.[7]

(b) In Aqueous Base. The above amounts of **1a** and bromine were added to an aqueous solution containing 1 equiv of KOH. This resulting solution turned red and then black! After a few hours black needles were deposited which were identified from their IR spectra as **5a** (85% yield).

(c) In Water. Over a 5-min period bromine (3.2 g, 20 mmol) in 40 mL of 1 M aqueous KBr was added with stirring to **1a** (1.9 g, 20 mmol) in 20 mL of 1 M aqueous KBr. After 24 h this solution deposited crystals which were filtered off and recrystallized from acetonitrile to give 2.72 g (78%) of 3-bromo-2-pyridone (**3a**), identified by its NMR and IR spectra.[7] Methylation of this material with dimethyl sulfate (as above for **3a** → **3b**) gave **3b** as required.

Bromination of 1-Methyl-2-pyridone (1b) in Acid Solution. 1b (0.73 g, 6.7 mmol) was dissolved in 10 mL of an aqueous solution which was 0.1 M in $HClO_4$ and 1 M in KBr. To this solution was added with stirring bromine (1.07 g, 6.7 mmol) in 10 mL of the same medium. After the solution was left to stand for 3 h 0.6 g (67%) of the 3,5-dibromo product **5b** crystallized out. Its IR spectrum was identical with that reported.[7]

Acknowledgment. The authors thank the Natural Sciences and Engineering Research Council of Canada for operating grants to O.S.T. and a postgraduate scholarship to M.P.

Registry No. 1a, 142-08-5; **1a**·Na, 930-70-1; **1b**, 694-85-9; **1b**·HBr, 1121-27-3; **2b**, 1628-89-3; **3a**, 13466-43-8; **3b**, 81971-38-2; **4a**, 13466-38-1; **4a**·Na, 13472-92-9; **4b**, 81971-39-3; **5a**, 13472-81-6; **5b**, 14529-54-5; **6**, 13472-85-0.

Supplementary Material Available: Rate constants for reaction of bromine with **1a** (Table S1), **1b** (Table S2), **2b** (Table S3), and **3a**, **3b**, **4a**, and **4b** (Table S4) (5 pages). Ordering information is given on any current masthead page.

Time-Resolved and Steady-State Fluorescence Studies of the Excited-State Proton Transfer in 3-Hydroxyflavone and 3-Hydroxychromone

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Abstract: The 2-methyltetrahydrofuran (MTHF) solution of 3-hydroxyflavone (3-HF) exhibits dual fluorescence at room temperature due to the normal form (N*) of 3-HF and the tautomer (T*) generated from N* by the excited-state proton transfer. The fluorescence rise time of the T* fluorescence was in good consistency with the N* fluorescence decay time. The activation energy and the Arrhenius factor were determined to be ca. 2.9 kcal mol^{-1} and 3.3 × 10^{12} s^{-1}, respectively, from the temperature dependence of the intensity ratio and lifetimes of dual fluorescence. Furthermore, the temperature dependence of the fluorescence lifetime of T* yields an activation barrier of 4.1 kcal mol^{-1} for the nonradiative decay process of T*. The MTHF solution of 3-hydroxychromone (3-HC) exhibits neither N* nor T* fluorescence. The 3-methylpentane (MP) solution of 3-HC exhibits only T* fluorescence at room temperature to ~180 K. The fluorescence rise time of T* in 3-HC was too fast to be determined by nanosecond pulse excitation, though the rise time in 3-HF was observed to be ~1-0.5 ns at 160-195 K. The difference of the fluorescence behavior between 3-HF and 3-HC was discussed in terms of the effect of the phenyl group of the γ-pyrone ring on the excited-state proton transfer and the stabilization of the tautomer form (T*).

A large number of studies have been reported on the intramolecular proton-transfer reaction. In recent years, kinetic studies with picosecond spectroscopy have revealed the following facts.[2-7] (a) Intramolecular excited-state proton transfer occurs very rapidly, usually faster than 10 ps. (b) In most cases, the pro-

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(2) Shizuka, H.; Matsui, S.; Hirata, Y.; Tanaka, I. *J. Phys. Chem.* **1976**, *80*, 2070; **1977**, *81*, 2243 and references therein.

0002-7863/82/1504-4146$01.25/0