Kinetics and mechanism of the bromination of 4-pyridone and related derivatives in aqueous solution

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The kinetics of bromination of 4-pyridone and selected derivatives have been measured in aqueous solutions in the pH range 0–9, at 25°C. The tautomerie system 4-pyridone ⇄ 4-hydroxypyridine (**1***a* ⇄ **2***a*) reaets with bromine via the predominant (pyridone) tautomer at pH < 6 and via the conjugate anion at pH > 6. 3-Bromo-4-pyridone behaves similarly. The kinetics also reveal that the facile dibromination of 4-pyridone occurs because at most pH's the monobromo derivative is actually more reactive towards bromine by virtue of its lower pK_a values. From the point of view of reactivity the 4-pyridones and their anions behave as substituted phenoxide ions. 4-Methoxypyridine does not undergo bromination under comparable conditions, but rather forms a complex with bromine.

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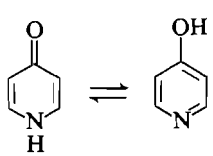
On a mesuré les cinétiques de la bromation de la pyridone-4 et de quelques dérivés en solutions aqueuses et dans un intervalle de pH allant de 0 à 9, à 25°C. Le système tautomère pyridone-4 ⇄ hydroxy-4 pyridine (**1***a* ⇄ **2***a*) réagit avec le brome par l'intermédiaire du tautomère prédominant (pyridone) à un pH < 6 et par l'intermédiaire de l'anion conjugué à un pH > 6. La bromo-3 pyridone-4 se comporte de la même façon. La cinétique révèle également que la débromation facile de la pyridone-4 se produit parce qu'à plusieurs pH le dérivé monobromé est actuellement plus réactif vis-à-vis du brome en raison de ses pK_a's plus faibles. Du point de vue de la réactivité, les pyridones-4 et leurs anions se comportent comme des ions phénoxydes substitués. La méthoxy-4 pyridine, dans des conditions comparables, n'est pas bromé, mais elle forme de préférence un complexe avec le brome.

[Traduit par le journal]

Introduction

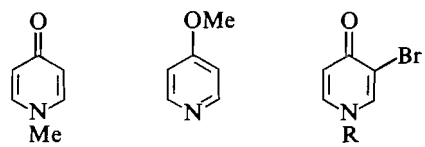
Pyridones react readily with halogens or halogenating agents in various media (1). The reactions are so facile that 3,5-disubstitution is almost always observed, and useful clean monohalogenation has rarely been reported (1, 2). We recently showed that monobromination of 2-pyridone can be achieved in aqueous solution by controlling the pH of the medium (3). This was made possible by a kinetic study of the bromination of 2-pyridone and selected derivatives over a wide range of pH. We ascertained the reactive forms of 2-pyridone and the relative reactivities of its monobromo derivatives and their reactive forms. This information enables the choice of conditions such that the second bromination is slow relative to the first (3).

The present paper reports an analogous study of the aqueous bromination of 4-pyridone (**1***a*). In it we likewise ascertain the reactive forms of the substrate and probe the origins of its facile dihalogenation. As a result, we show how its monobromination can be carried out relatively easily. In contrast, other routes to 3-bromo-4-pyridone are long and give poor overall yields.



1*a* **2***a*

In the vapour phase and in dilute nonpolar solution the tautomeric equilibrium **1***a* ⇄ **2***a* favours 4-hydroxypyridine (**2***a*). However, in aqueous solution the pyridone tautomer **1***a* predominates by a factor of ~2000:1 (4). Nevertheless, in principle the aqueous bromination of 4-pyridone could take place upon the minor tautomer if this was sufficiently reactive. Therefore, in order to find out which of the tautomers is the reactive form we have studied the bromination of the tautomeric system **1***a* ⇄ **2***a*, and of the methyl derivatives, 1-methyl-4-pyridone (**1***b*) and 4-methoxypyridine (**2***b*).



1*b* **2***b* **3***a*, R = H
3*b*, R = Me

To gain insight into the facile dihalogenation of 4-pyridone we have also studied the bromination of 3-bromo-4-pyridones **3***a* and **3***b*. As with our previous study, the speed of the reactions rules out conventional means of following the kinetics, and so we have used stopped-flow uv spectrophotometry (3, 5).

Results

All of the substrates studied react fairly quickly with bromine in water and undergo bromination, with the exception of 4-methoxypyridine, **2***b*. This substrate reacts to form a 1:1 complex with bromine which impedes normal electrophilic bromination of **2***b* (see Experimental).

Kinetic studies

The four remaining substrates (**1***a*, **1***b*, **3***a*, **3***b*) were studied in reaction with bromine in aqueous media in the pH range 0–9 using the same methods as earlier (3, 5). For the most part a large excess of substrate over bromine was employed, and under these conditions the disappearance of bromine was cleanly first-order. Rate constants (k_1^{obs}) obtained from analysis of the absorbance data increased linearly with substrate concentration, but were independent of the initial bromine concentration. Thus we conclude that at any given pH the reaction of

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TABLE 1. Rate constants for reactions of bromine with 4-pyridones in 1 *M* KBr at 25°C

S	pH	$[S] \times 10^4$, (*M*)	$[Br_2] \times 10^5$, (*M*)	k_1^{obs}, (s^{-1})	k_2^{obs}, (M^{-1} s^{-1})
1*a*[a]	1.12[b]	15.29	5.0	—	44.8
	1.45	20.0	5.0	0.0102	88.5
	2.08[b]	1.529	5.0	—	397
		3.824	5.0	—	426
		7.647	5.0	—	400
	2.35[b]	7.647	5.0	—	844
	3.17[b]	7.647	5.0	—	3720
	3.30	20.0	5.0	0.410	3580
	3.80	10.0	5.0	0.371	6630
	4.90	10.0	5.0	0.614	11000
	5.52	10.0	5.0	0.683	12200
	5.56	10.0	5.0	0.852	15200
	6.24	10.0	5.0	2.06	36800
	6.50	10.0	5.0	2.14	38300
	6.93	10.0	5.0	6.27	113000
	7.40	20.0	5.0	33.1	293000
	7.92	10.0	5.0	39.1	738000
	8.74	5.0	5.0	0.113	6710000
1*b*[c]	1.10	25.0	5.0	0.00598	41.5
	2.25	5.0	5.0	—	597
		12.5	5.0	—	597
	3.12	5.0	5.0	0.0888	3360
	3.31	5.0	5.0	0.113	4280
	3.96	5.0	5.0	0.243	9560
	4.96	5.0	5.0	0.308	11600
	5.97	5.0	5.0	—	13300
		7.5	5.0	—	13200
	6.92	5.0	5.0	—	12800
3*a*	0.08	10.0	2.5	0.00171	29.9
	0.66	5.0	2.5	0.00262	93.9
	1.90	5.0	2.5	0.0130	465
	2.37	2.5	2.5	0.00784	592
	3.00	5.0	2.5	0.0224	802
	3.41	2.5	2.5	0.0121	914
	4.03	2.5	2.5	0.0184	1390
	4.75	1.25	2.5	0.0145	2470
	5.26	2.5	2.5	—	7560
		5.0	2.5	—	7860
	5.95	2.5	2.5	0.295	22300
	6.25	2.5	2.5	0.508	38300
	7.18	1.25	2.5	3.05	522000
		2.5	2.5	6.66	507000
	7.61	2.5	2.5	15.2	1170000
	8.00	2.5	2.5	35.7	2850000
3*b*	0.50	20.0	5.0	0.00389	43.9[d]
	1.00	20.0	5.0	0.0119	114 [d]
	1.50	8.0	5.0	0.0106	240
	2.00	12.0	5.0	0.0250	369
		20.0	5.0	0.0449	391
		28.0	5.0	0.0618	382
	3.34	20.0	5.0	0.0567	494
	4.91	20.0	5.0	0.0658	573
	6.28	20.0	5.0	0.0644	562
	7.32	8.0	5.0	0.0263	602
	8.50	20.0	5.0	0.0476	537

[a]Introduced as HNO_3 salt.
[b]Introduced as sodium salt dihydrate.
[c]Introduced as HBr salt.
[d]Correction for Br^- includes contribution from KBr + HBr.

bromine with the substrates follows a second-order rate law. Accordingly, the observed values of k_1^{obs} were converted to

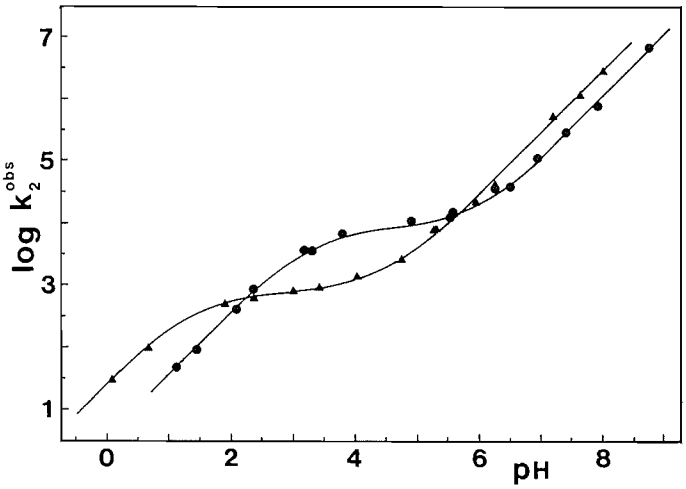


FIG. 1. pH–rate profiles for reaction of aqueous bromine with 4-pyridone **1***a* (circles) and 3-bromo-4-pyridone **3***a* (triangles) at 25°C, I = 1.0 *M* (KBr).

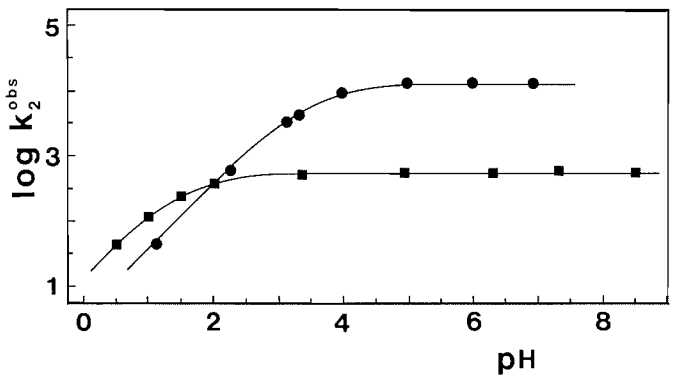


FIG. 2. pH–rate profiles for reaction of aqueous bromine with 1-methyl-4-pyridone **1***b* (circles) and 3-bromo-1-methyl-4-pyridone **3***b* (squares) at 25°C, I = 1.0 *M* (KBr).

second-order rate constants (k_2^{obs}), taking into account the substrate concentration and the depletion of free bromine due to the formation of tribromide ion, hypobromous acid, and its anion (see Experimental).

The observed rate constants are collected in Table 1, and displayed in Figs. 1 and 2. In many cases the absorbance data were also analyzed directly for second-order behaviour (5*c*). The rate constants (k_2^{obs}, after correction for the free bromine concentration) thus obtained were generally in good agreement with those derived from k_1^{obs} values. In Table 1, where no entry is given for k_1^{obs}, the value of k_2^{obs} was obtained solely from second-order analysis (5*c*).

The observed pH–rate profiles (Figs. 1 and 2) are very similar to those obtained earlier for the analogous 2-pyridones (3). The *N*-methyl derivatives **1***b* and **3***b* show profiles (Fig. 2) appropriate for reaction upon their free base forms, since the literature protonation pK for **1***b* is 3.33 (6) and that for **3***b* we have measured to be 1.52. For such behaviour (eq. [1]) the appropriate form of the observed rate constant is given by

$$[1]\quad SH^+ \overset{K_1}{\rightleftharpoons} S \xrightarrow[Br_2]{k_2} \text{products}$$

$$[2]\quad k_2^{obs} = k_2K_1/(K_1 + [H^+])$$

eq. [2]. The calculated curves in Fig. 2 were generated from eq. [2] using the values of k_2 and K_1 (expressed as pK_1) given

TABLE 2. Constants for reaction of bromine with 4-pyridones in aqueous solution (25°C, I = 1.0 M (KBr))

Substrate	pK_1 meas.	pK_1 fitted	pK_2	k_2 (M^{-1} s^{-1})	$k_2'K_2$ (s^{-1})	k_2' (M^{-1} s^{-1})
1*a*	3.27[a]	3.46	11.09[a]	10100	0.0110	1.35×10^9
1*b*	3.33[a]	3.58	—	12800	—	—
3*a*	1.37[b]	1.53	9.46[c]	791	0.0287	8.28×10^7
3*b*	1.52[b]	1.58	—	549	—	—

[a]At 20°C, from ref. 6.
[b]This work, at 25°C, and I = 0.15 M ($HClO_4$ + $NaClO_4$).
[c]This work, at 25°C, and I = 0.1 M (KBr).

in Table 2. The fitted values of pK_1 (3.58 and 1.58) are in good agreement with the measured values (3.33 and 1.52).

The data for 4-pyridone **1***a* and its 3-bromo derivative **3***a*, which are shown in Fig. 1, cannot be solely explained by eqs. [1] and [2]. Clearly in each case another process takes over at the higher pH's which we believe to be reaction upon the conjugate anions of the substrates. Such behaviour was observed earlier for 2-pyridones (3). For this situation (eq. [3]) the expected variation of k_2^{obs} with acidity is given by eq. [4].

[3] $$SH_2^+ \overset{K_1}{\rightleftharpoons} SH \overset{K_2}{\rightleftharpoons} S^-$$
$$k_2 \downarrow Br_2 \qquad k_2' \downarrow Br_2$$
$$\text{products}$$

[4] $$k_2^{obs} = \frac{k_2K_1}{(K_1 + [H^+])} + \frac{k_2'K_2}{[H^+]}$$

The simplicity of the second term in this equation is warranted at the pH's employed, since for 4-pyridone pK_2 = 11.09 (6) and for 3-bromo-4-pyridone we have measured pK_2 = 9.46.

From Fig. 1 and the calculated curves shown therein, it is clear that eq. [4] gives an excellent representation of the data for the substrates **1***a* and **3***a*. The appropriate parameters are again collected in Table 2.

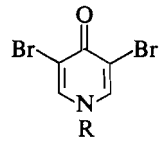
In summary, the reaction of bromine with the 4-pyridones **1***a*, **1***b*, **3***a*, and **3***b* over the pH range 0–9 apparently involves attack upon the free base form and upon the conjugate anions of **1***a* and **3***a* at higher pH (see Fig. 1).

Product studies

As noted above, and detailed in the experimental section, 4-methoxypyridine **2***b* does not undergo normal electrophilic bromination, but rather forms a relatively stable complex with bromine. This complex is obtained whether the solvent is water, ethanol, or chloroform. It brominates acetone in chloroform and **2***b* is recoverable as its hydrobromide salt.

Attempted bromination of 4-pyridone **1***a* in concentrated hydrobromic acid gave a 73% yield (based on bromine) of 3,5-dibromo-4-pyridone **4***a*. Proton magnetic resonance analysis of the mother liquor revealed a 2:5 ratio of **3***a*/**1***a*. Likewise, bromination of **1***a* in unbuffered 1 M aqueous KBr gave a 67% yield of **4***a*. When this reaction was repeated in the presence of one equivalent (to **1***a*) of KOH the yield of **4***a* was 86%. In all cases, 3-bromo-4-pyridone **3***a* was only a minor product of reaction.

We also carried out various other bromination reactions employing different reagents and solvents. In all cases the dibromo derivative **4***a* was the major product, with yields of 60–72% (see Experimental).



4*a*, R = H
4*b*, R = Me

After we had obtained the kinetic data shown in Fig. 1 it seemed likely that the best chance of monobrominating 4-pyridone was in aqueous solution buffered in the region pH 3–5, the only region where the rate profile of **1***a* rises above that of **3***a*. Accordingly, bromine in aqueous KBr was slowly added to an equivalent amount of 4-pyridone in water buffered with sodium acetate/acetic acid to pH 4.2–4.4. From solution there precipitated a 26.2% yield of the dibromo compound **4***a*, but the mother liquor contained **3***a* (73.8%) and the appropriate amount of **1***a* (26.2%). After purification and recrystallization we obtained a 28% yield of the desired 3-bromo-4-pyridone, **3***a*. No optimization was attempted, but probably with stronger buffering and improved separation of the product mixture a higher isolated yield of **3***a* could be obtained.

Other routes to **3***a*

At the outset various attempts were made to synthesize **3***a* unambiguously using routes based directly or indirectly on literature precedents. With one exception they were unsuccessful due to reactions giving no product or an undesired product. The successful exception involves a multistep route in which the last step gave a very poor yield of the desired product. 3-Bromopyridine (7) was converted to its *N*-oxide (8) which was then nitrated to 3-bromo-4-nitropyridine-*N*-oxide by a modification of literature procedures (9, 10). Simultaneous reduction of the nitro group and the *N*-oxide moiety by iron and acetic acid (11) gave 3-bromo-4-aminopyridine. After several attempts, hydrolysis of this product by diazotization (12) produced only 3% of the desired 3-bromo-4-pyridone, **3***a*.

3-Bromo-4-nitropyridine was made by deoxygenation (13) of its *N*-oxide (*vide supra*). An attempt to hydrolyse it to **3***a* with aqueous barium hydroxide (14) failed. Hydrolysis in refluxing aqueous sulphuric acid gave material which had some of the characteristics of **3***a*, but the melting point was 125° too low!

Bromination of 4-hydroxypyridine-*N*-oxide, according to the procedure of Hayashi (15), gave the 3,5-dibromo derivative and not the desired 3-bromo product, as reported (15). Likewise, attempted monobromination of chelidamic acid (4-pyridone-2,6-dicarboxylic acid) gave the undesired dibromo derivative.

Monobrominations of 4-aminopyridine and of 4-dimethylaminopyridine were also not successful due to the formation of complexes with the halogen (16).

Clearly, on the basis of our experience, the best approach to 3-bromo-4-pyridone **3***a* is to use direct bromination of 4-pyridone in an aqueous medium strongly buffered at pH 4.

Discussion

Reactive forms

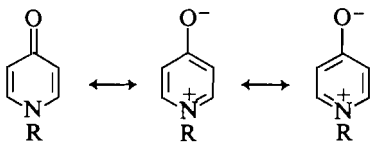
Over the pH range 0–5 the rate profiles of 4-pyridone **1***a* and its *N*-methyl derivative **1***b* are virtually superimposable. This is reflected in Table 2 by their very similar values of k_2. In contrast, the *O*-methyl derivative **2***b* shows quite different behaviour towards bromine. Given that the pyridone tautomer **1***a* greatly predominates in aqueous solution (4), our results provide compelling evidence that 4-pyridone **1***a* reacts with bromine as its major tautomer and not via the minor hydroxy tautomer **2***a*, at pH < 6. At higher pH the rate of bromination of **1***a* increases in a manner appropriate for reaction upon its conjugate anion (eq. [4], Fig. 1).

In the same way, the reactivity of the monobromo derivatives **3***a* and **3***b* are very similar at low pH, consistent with **3***a* reacting as such. Above pH > 3.5, **3***a* apparently reacts with bromine via its anion.

Our results complement those of Katritzky and co-workers for the nitration in strong acid and the deuterium exchange of 4-pyridone at high temperatures (17, 18). Nitration takes place upon the free base pyridone tautomer except at higher acidities where the conjugate acid reacts (17). Hydrogen isotope exchange apparently only involves the free base form (18).

Reactivities

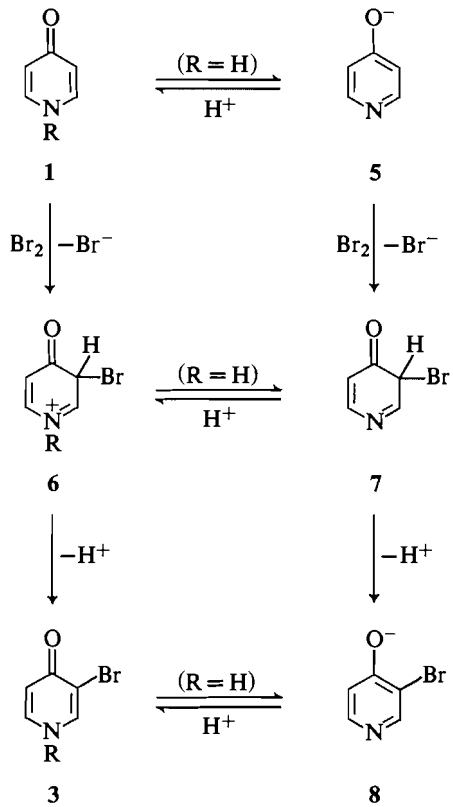
For 2-pyridones and their anions we showed that they react with bromine at rates expected for substituted phenoxide ions (3). This correlation is rationalized by consideration of the dipolar valence-bond structures which contribute to a pyridone. In the case of the 4-pyridones **1**, there must be significant contributions from the structures **1′** and **1″**, as Acheson emphasizes (19). They can account for various properties of **1***a* (19),



1 **1′** **1″**

including the solvent dependence of its tautomerism (4) and its reactivity in deuterium exchange (18). The structures **1′** and **1″** suggest that 4-pyridone can be considered as phenoxide ion bearing a *para* azonium nitrogen (=$\overset{+}{N}$H—) as substituent. Of course, the anion of **1***a* is phenoxide ion with a *para* aza nitrogen (=N—).

Using literature values of σ_m^+ for azonium nitrogen (2.00), aza nitrogen (0.54), and bromine (0.41) (3, 20, 21) the rate data for **1***a*, **3***a*, and their respective anions give a good correlation (r = 0.9987) with $\rho^+ = -3.43$. This is similar to the value of −3.83 for 2-pyridones and their anions (3) and the value of −3.5 for phenoxide ions estimated by Kulic and Vecera (22). It adds further weight to the idea that, with respect to reactivity, pyridones and their anions behave as substituted phenoxides.



SCHEME 1

Mechanism

Our data can be explained by the simple pathways set out in Scheme 1. In acidic solution **1** (*a* or *b*), in equilibrium with its protonated form, is attacked by bromine to give the transient cation **6** which is deprotonated to form the product **3**. In the case where R = H the cation **6***a* may also deprotonate to the neutral azacyclohexadienone **7**. However, we see no evidence of the build-up of any intermediates during the reaction.[2] Therefore we surmise that acid- or base-catalyzed tautomerization of **7** to **3***a* is relatively fast.[3]

At higher pH 4-pyridone **1***a* reacts via its anion **5** to give directly the azacyclohexadienone **7**. Again, tautomerization of this intermediate (**7** → **8** → **3**) is presumed to be fast.[3] This pathway is analogous to that followed by phenols which react via their anions, except at high acidities (22, 23).

The brominations of **3***a* and **3***b* show similar rate profiles to those of **1***a* and **1***b*. Therefore we propose that they occur by mechanisms analogous to those set out in Scheme 1.

[2]We have observed the formation of relatively long-lived intermediates during the bromination of pyrimidones, uracils, and cytosines (5).

[3]Available evidence in the literature suggests that cyclohexadienones are not observable in the aqueous bromination of phenols. Kulic and Vecera found that bromine decrease and product increase occur at the same rate for various *para* substituted phenols (22). However, we have recently shown that 4-bromo-2,5-cyclohexadienones are observable in the aqueous bromination of simple phenols. On the other hand, we cannot detect any intermediates from phenols bearing electron-withdrawing groups or the cyclohexadienones derived from *ortho* bromine attack. In these cases tautomerization to the aromatic product is almost certainly too fast (39).

The principal active electrophile in the brominations of **1** and **3** is almost certainly molecular bromine, as depicted in Scheme 1. Tribromide ion is present in significant concentration under the conditions used. However, it is a much weaker electrophile in general (24), and for highly reactive phenoxide ions its reactivity is only about 1% of that of bromine (23). It is probable, therefore, that Br_3^- only makes a contribution where 4-pyridone is reacting via its anion **5**.

Other potential electrophiles are hypobromous acid (HOBr) and its protonated form (H_2OBr^+) (24). The former is much less reactive than bromine and its concentration is very low under our conditions, excepts at the higher pH's. Moreover, the observed pH dependences are inconsistent with its involvement. The concentration of the much more reactive electrophile H_2OBr^+ must be extremely low, given the low concentration of HOBr. For it to be involved in the reaction of the anions of **1***a* and **3***a* would required rate constants above diffusion-controlled (25).

Disubstitution

The reasons behind the facile dibromination of 4-pyridone **1***a* are easily seen by referring to Fig. 1 and Table 2. Except for the relatively small range of pH 2.5−5.5, 3-bromo-4-pyridone **3***a* is effectively more reactive than **1***a* (Fig. 1). This apparently anomalous situation arises because of the relationships between the values of k_2K_1 and k_2K_2 for the two substrates.

At pH < 2, where both **1***a* and **3***a* are significantly protonated, the difference in reactivity of **1***a* and **3***a* (factor of 12) is more than offset by the difference in K_1 values (factor of 85). Likewise at pH > 5.5, where reaction upon the conjugate anions predominates, the higher reactivity of the anion of 4-pyridone is more than compensated for by the larger value of K_2 for **3***a*.

Even at pH 4, where the rate profile for **1***a* is significantly above that for **3***a*, reaction upon **1***a* is only favored by a factor of about 6.3 (Fig. 1). Therefore, in a 1:1 reaction of bromine with 4-pyridone **1***a*, by the time of 86% reaction the product **3***a* effectively competes with **1***a* for bromine, and a significant amount of dibromo product **4***a* will result. Seen in this light, our 26% yield of **4***a* from a reaction buffered around pH 4.3 is not surprising.

The literature contains a preparative iodination of 4-pyridone, carried out with iodine in aqueous potassium iodide (26). This procedure leads to a 50% yield of the 3-iodo derivative, as well as 21% of the 3,5-diiodo compound. Presumably similar factors are involved here as in the bromination reaction, and so one can anticipate similar rate profiles. A higher yield of the monoiodo product might be obtained by using a medium buffered around pH 4.

Experimental

Kinetic methods

The stopped-flow apparatus, data acquisition, and data analysis were as in other recent work (3, 5). All kinetics solutions were 1.0 *M* in potassium bromide and, except for the highest acidities, I = 1.0 *M*. For pH > 1 a "universal buffer" was used as before (3). Reactions were followed as bromine disappearance by monitoring the tribromide ion band near 265 nm. Temperature control was obtained by circulation of water from a Lauda constant temperature bath kept at 25.0 ± 0.1°C.

The second-order rate constants (k_2^{obs}) given in the main text have been corrected for the actual free concentration of bromine. This is less than the total concentration of bromine due to the formation of tribromide ion and, at higher pH, of hypobromous acid (5*a*). In the present work, since higher pH's were employed than earlier, it was also necessary to correct for the ionization of HOBr.

The relevant equilibria are:

$$Br_3^- \overset{K_1}{\rightleftharpoons} Br^- + Br_2$$

$$Br_2 + H_2O \overset{K_2}{\rightleftharpoons} H^+ + Br^- + HOBr$$

$$HOBr \overset{K_3}{\rightleftharpoons} H^+ + {}^-OBr$$

From $[Br_2]_t = [Br_2] + [Br_3^-] + [HOBr] + [{}^-OBr]$ and the definition of K_1, K_2, and K_3 one can easily derive the equation for the correction factor, as given below in eq. [5].

$$[5] \quad \frac{[Br_2]_t}{[Br_2]} = 1 + \frac{[Br^-]}{K_1} + \frac{K_2}{[H^+][Br^-]} + \frac{K_2K_3}{[H^+]^2[Br^-]}$$

The appropriate values of the constants are K_1 = 0.0625 *M* (27), $K_2 = 9.6 \times 10^{-9}$ M^2 (28), and $K_3 = 2.06 \times 10^{-9}$ *M* (29). Apparent second-order rate constants, either from direct analysis or from pseudo first-order rate constants, were multiplied by the factor in eq. [5] to give values of k_2^{obs}. Those given in the text are averages of 3−5 runs. The validity of the corrections for HOBr and OBr^- is supported by the lack of systematic deviations in the rate profiles at the higher pH's.

*p*K *measurements*

These were made by the normal spectrophotometric method (30), at 25°C. For **3***a* we obtained pK_1 = 1.37 ± 0.01, pK_2 = 9.46 ± 0.02, and for **3***b* we found pK_1 = 1.52 ± 0.02. Ionic strength was 0.1 *M* or 0.15 *M*, as given in Table 2. For future use we also measured pK_1 = 7.14 ± 0.02 (I = 0.1 *M*) for 4-amino-3-bromopyridine.

Substrates and products

The compounds used in this study are known from the literature. Accordingly, in the following we provide details only for those procedures which differed from the literature either in execution or in outcome. Elemental analyses were performed by Galbraith Labs. Inc., Knoxville, Tennessee.

*4-Pyridone (1*a*)*

This substance is difficult to purify and to keep pure. Therefore we made use of salts, since this approach worked well in earlier work (3).

Compound **1***a* (Aldrich, technical grade) was dissolved in ethanol and decolourized with charcoal. To the clear filtrate was added one equivalent of sodium ethoxide, and the *sodium salt* was precipitated with acetone. Three recrystallizations from 10:1 CH_3CN/EtOH gave white needles, mp 96−97°C. Spinner and White (31, 32) reported this compound but gave no melting point. Proton magnetic resonance in D_2O and in DMSO-d_6 suggested two waters of crystallization, but the elemental analysis was poor. *Anal.* calcd. for $C_5H_4NONa \cdot 1.25\ H_2O$: C 43.14, H 4.71, N 10.06; found: C 43.42, H 5.76, N 10.15.

Initial kinetic studies were carried out with the above material. However, the *nitrate salt* proved to be a superior alternative which was used for the remainder of the kinetic work. It was initially produced by accident during an attempted nitration following Albert and Barlin (33). 4-Hydroxypyridinium nitrate was extracted from the salts with ethanol, decolourized with charcoal, and twice recrystallized from water, mp 198−200°C (dec). *Anal.* calcd. for $C_5H_6N_2O_4$: C 37.98, H 3.82, N 17.72; found: C 37.94, H 3.95, N 17.58. The same nitrate salt was more conveniently prepared by acidifying a concentrated aqueous solution of **1***a* with nitric acid to pH 1. After standing, the material which crystallized out was treated as above. It gave an identical ir spectrum and mp.

*1-Methyl-4-pyridone (1*b*) hydrobromide salt*

Compound **1***a* (practical grade) was partially dehydrated and purified by heating with two equivalents of hexamethyldisilazane in chloroform. Solid material was filtered off and the filtrate was reduced to half its original volume. Addition of ether gave white flakes of a hydrate of **1***a*, mp 66−67°C (sublimed **1***a* has mp 148−149°C) (18).

To this hydrate (7.6 g, 68 mmol) and sodium methoxide (3.7 g, 68.5 mmol) in 10 mL methanol was added, with stirring, dimethyl

sulphate (8.83 g, 70 mmol) in 10 mL methanol. The solution was heated for 15 min and then the pH was adjusted to 7–8 with sodium bicarbonate. Repeated addition and evaporation with 1:1 acetone/chloroform precipitated the salts which were filtered off. The filtrate was reduced to give an oil which was dissolved in acetone containing a slight excess of concentrated hydrobromic acid. Evaporation of the solvent gave the hydrobromide salt (6 g, 46%), recrystallized from methanol/ether, mp 175–177°C (when dried at 110°C for 1 hour). *Anal.* calcd. for C_6H_8BrNO: C 37.92, H 4.24, N 7.37, Br 42.05; found: C 37.80, H 4.16, N 7.22, Br 41.95.

*4-Methoxypyridine (2*b*)*

To 4-methoxypyridine-*N*-oxide (Aldrich) was slowly added 2 equivalents of phosphorus trichloride and a vigorous reaction ensued. The solution was stirred for 20 min and then made slightly alkaline with concentrated aqueous ammonia. The resultant solution was extracted 3 × 100 mL of chloroform and the dried extracts (Na_2SO_4) were evaporated to give an 85% yield of **2***b*. The proton nmr agreed with the literature (34).

4-Methoxypyridine: bromine complex

Addition of bromine to **2***b* in water, ethanol, or in chloroform precipitated a complex. From water the complex was yellow, mp 120–121°C; from chloroform it was red, mp 117–119°C. The proton nmr spectra of these materials were similar to that of **2***b*.

The complex brominated acetone in chloroform and gave back **2***b* as its HBr salt. Its ir spectrum was identical to that of the hydrochloride salt (34). Upon heating the bromine complex in water, bromine vapour was evolved and no bromination of **2***b* was detected.

*3-Bromo-4-pyridone (3*a*)*

(a) *From 4-amino-3-bromopyridine* (see below)

Diazotization of this compound employing the procedure of Talik (12) gave only a 3% yield after several attempts.

(b) *From bromination of 4-pyridone (1*a*)*

4-Pyridone (0.95 g, 10 mmol) was dissolved in 50 mL water containing sodium acetate (1 g, 12 mmol) and the pH was adjusted to 4.2–4.4 with acetic acid. This solution was cooled in ice, and bromine (1.6 g, 10 mmol) in 50 mL 1 *M* aqueous KBr was added, with stirring, over 45 min. A precipitate of dibromo compound **4***a* (0.33 g, 26.2% based on bromine) was filtered off and the filtrate was evaporated to dryness. The residue, containing inorganic salts and organics, was extracted with ethanol and the extract was evaporated. The solid residue contained a 4:1 mixture of **3***a* and **1***a*, from its ^{1}Hmr spectrum. To effect further separation from salts the residue was treated with boiling acetone. The hot solution was filtered and reduced to dryness to give 1.55 g of solid which contained 80% 3-bromo-4-pyridone **3***a* (73.8%, based on bromine) and 20% unreacted 4-pyridone **1***a*. Decolourization with charcoal and recrystallization from boiling water gave **3***a* (0.48 g, 28% isolated yield), mp 229–231°C (lit. (9) mp 228–230°C).

No optimization was attempted. Doubling the concentrations of the reactants caused a 1.6-fold increase in the percent formation of the undesired dibromo product **4***a*.

Attempted brominations of 4-pyridone

(a) *In acid*

To 4-pyridone (0.95 g, 10 mmol) in 25 mL of concentrated HBr was added, with stirring, an equivalent amount of bromine in 25 mL of the same acid, over 30 min. Ice was added and the pH brought to 3 with sodium carbonate. The solution was reduced in volume on a water bath and, upon cooling, 0.923 g of 3,5-dibromo-4-pyridone (**4***a*) crystallized out (73% yield, based on bromine). Its ir spectrum matched that in the literature (35). The ^{1}Hmr analysis of the solid from evaporating the filtrate showed a 2:5 mixture of **3***a* and unreacted **1***a*.

(b) *In 1* M *aqueous KBr*

The above procedure again yielded **4***a* (0.842 g, 67%).

(c) *In base*

The same procedure in 1 *M* aqueous KBr containing 1 equivalent of KOH precipitated **4***a* (1.08 g, 86%). Both here and in (b) **3***a* was a minor product.

(d) *In dioxane*

"Dioxane dibromide" is considered a mild brominating agent (36). However, mixing equimolar quantities of bromine and **1***a*, each in dioxane, slowly precipitated **4***a* (60% yield).

(e) *Pyridinium hydrobromide perbromide* (37) and **1***a* in $CHCl_3$ gave **4***a* (72%).

(f) *2,4,4,6-Tetrabromo-2,5-cyclohexadienone* is another mild brominating agent (38). From a 1:1 reaction with **1***a* in $CHCl_3$ at 0°C we again obtained **4***a* (65%).

*Other routes to 3*a

Various other attempts to make **3***a* were unsuccessful, as outlined in the text. These failed either because of a recalcitrant hydrolysis step, or due to attempted monobromination again giving undesired dibromination.

4-Amino-3-bromopyridine

3-Bromopyridine was obtained from Aldrich and by diazotization of 3-aminopyridine (74% yield) (7). It was oxidized in 90–93% yield (8), and the *N*-oxide was nitrated as follows.

3-Bromopyridine-*N*-oxide hydrochloride (8) (35 g, 0.166 mmol) dissolved in 35 mL concentrated H_2SO_4 was poured into a mixture of KNO_3 (32 g), concentrated HNO_3 (54 mL), concentrated H_2SO_4 (42 mL), and 20% oleum (28 mL). The solution was heated slowly to 100°C and held there for 21 h. The cooled solution was treated with ice and sodium carbonate, and finally brought to pH 7–8 with aqueous ammonia. After cooling in ice for 20 min the solid from the mixture was filtered off and dried in air. The desired 3-bromo-4-nitropyridine-*N*-oxide (25.1 g, 70%) was extracted from the solid with boiling $CHCl_3$ and was recrystallized from benzene, mp 150–152°C (lit. (8) mp 152–152.5°C, 58%).

The above product was reduced by a procedure modified from the literature (11). 3-Bromo-4-nitropyridine-*N*-oxide (5.0 g, 22.8 mmol) was dissolved in 100 mL acetic acid containing iron powder (8.33 g) in apparatus fitted with fast mechanical stirring. Gentle heat was applied to bring the temperature to 80°C. After 10 min the exothermic reaction brought the temperature to 110°C and the heat source was temporarily removed until it fell back to 80°C. After 90 min at this temperature the solution was cooled and brought to pH 8 with sodium bicarbonate and then ammonium hydroxide. Extraction with ether (3 × 300 mL) and evaporation of the extract gave 4-amino-3-bromopyridine (3.42 g, 86.7%), mp 66–68°C from light petroleum (lit. (11) mp 66–68°C),

This compound has a protonation p*K* of 7.14 ± 0.02 (*vide supra*).

*3-Bromo-1-methyl-4-pyridone (3*b*)*

To **3***a* (1.5 g, 8.6 mmol) in 30 mL MeOH containing KOH (0.48 g) was added dimethyl sulphate (1.6 mL, 18 mmol), and the mixture was refluxed for 2 h. The cooled solution was made basic with sodium methoxide. Addition of acetone (200 mL) and ether (10 mL) precipitated salts. Further removal of salts was achieved by repeated treatment with chloroform/acetone. After solvent removal the residual oil was dissolved in $CHCl_3$, filtered, and the filtrate was evaporated. The resulting oil was dissolved in acetone and addition of a slight excess of concentrated HBr precipitated **3***b*, as *the hydrobromide salt* (1.57 g, 68%). Recrystallization from acetonitrile (1 g/300 mL) gave transparent needles, mp 253–255°C; ^{1}Hmr (D_2O/DSS) δ: 4.23 (s, 3), 7.13 (d, 1, $J_{5,6}$ = 7.0 Hz), 8.23 (q, 1, $J_{2,6}$ = 2.4 Hz), 8.64 (d, 1). *Anal.* calcd. for $C_6H_7NOBr_2$: C 26.80, H 2.62, N 5.21, Br 59.42; found: C 27.08, H 2.69, N 5.23, Br 59.48.

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