# The Mechanism of Bromination of 2(1*H*)-Pyrimidinone, its *N*-Methyl and *N,N'*-Dimethyl Derivatives in Aqueous Acidic Solution

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Rates of bromination at the 5-positions of the title compounds have been measured in aqueous sulfuric acid solutions. The reaction involves a rapid irreversible formation of a 5-bromo-4,6-dihydroxy-hexahydro-2-oxopyrimidine which undergoes slow acid-catalyzed conversion to the corresponding 5-bromopyrimidinone. If excess bromine is present the latter product reacts further to produce a 5,5-dibromo-4,6-dihydroxyhexahydropyrimidine.

Les vitesses de bromation des positions-5 dans les composés du titre ont été mesurées dans des solutions aqueuses d'acide sulfurique. La réaction implique la formation rapide irréversible de la bromo-5 dihydroxy-4,6 hexahydro oxo-2 pyrimidine qui se transforme lentement, sous une catalyse acide, en bromo-5 pyrimidinone correspondante. Ce dernier produit continue de réagir en présence d'un excès de brome, pour donner la dibromo-5,5 dihydroxy-4,6 hexahydro pyrimidine.

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Due to their biological and pharmacological importance, pyrimidines have been extensively studied from a synthetic standpoint (1) but only recently have mechanistic studies been forthcoming (2). As part of a study of the electrophilic substitution of heteroaromatic compounds Katritzky and co-workers (3, 4) studied deuteration at the 5-position of 2(1*H*)-pyrimidinone **1**($R^1$ = H), 1-methyl-2(1*H*)-pyrimidinone **1** ($R^1$ = Me), and the 1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium ion **2** ($R^1 = R^2$ = Me). They concluded that these exchanges occur via the covalent hydrates **3** ($R^1 = R^2$ = H) and **3**($R^1$ = Me; $R^2$ = H), and the pseudo-base **3** ($R^1 = R^2$ = Me), respectively. A subsequent study of the nitration of these same derivatives (5) showed that **1**($R^1$ = H) and **1**($R^1$ = Me) react as their free bases but that the cation **2**($R^1 = R^2$ = Me) is unreactive.

Following an earlier communication (6), we now present more complete results of a study of the bromination of these pyrimidines in aqueous sulfuric acid solutions. Initially it was found that **1**($R^1$ = H), **1**($R^1$ = Me), and the cation **2**($R^1 = R^2$ = Me; anion = $Cl^-$ or $HSO_4^-$) react rapidly with bromine in aqueous solution at room temperature. Removal of the water under reduced pressure followed by recrystallization of the solid residue gave the 5-bromo derivatives: **6**($R^1$ = H), **6**($R^1$ = Me), **5**($R^1 = R^2$ = Me; anion = $Br^-$). The facility with which the quaternary salts reacted also suggested the intermediacy of the pseudo-base **3**($R^1 = R^2$ = Me) and thus, by analogy, that the parent compound **1**(R = H) reacts via its covalent hydrate **3**($R^1 = R^2$ = H). The changes occurring during bromination were then monitored spectrophotometrically. Upon addition of aqueous bromine to an acidic solution of the cation **2**($R^1 = R^2$ = Me), the u.v. absorption of the latter disappeared immediately but only slowly was it replaced by absorptions appropriate to the 5-bromo cation **5**($R^1 = R^2$ = Me). Similar behavior is exhibited by the other substrates **1**($R^1$ = H or Me), namely, that the solution obtained from mixing equimolar quantities of solutions of these substrates and bromine had no significant absorption above 220 nm. These observations suggested the initial formation of nonaromatic adducts of the type **4** (see Scheme 1) for which there are precedents.

Barbieri *et al.* have isolated derivatives of the type **11** formed during the bromination of some 2-sulfonamidopyrimidines (7). Likewise the bromination of 1,3-dimethyluracil has been postulated (8) to occur via the intermediate **12**($R^1$ = Me; $R^2$ = H) and thymine reacts with bromine to form the 5-bromo-5-methylhexahydropyrimidine **12**($R^1$ = H; $R^2$ = Me) (9). Furthermore, with excess bromine uracils give 5,5-dibromo derivatives **12**($R^2$ = Br) (1, 2).

Attempts to isolate and characterize the adducts **4** failed, giving white labile materials

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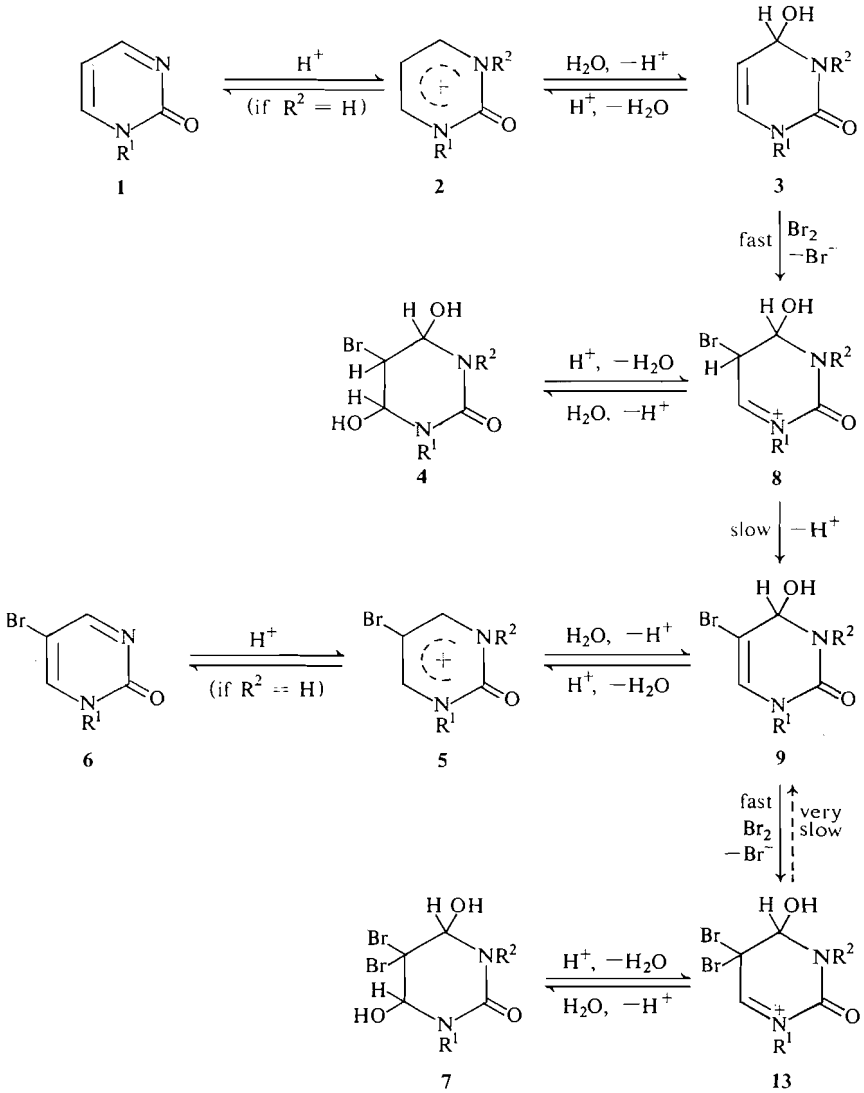
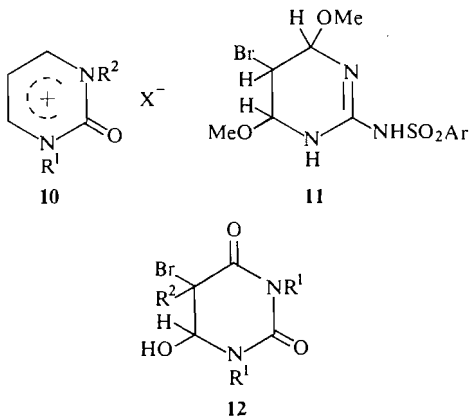



SCHEME 1



which readily transform to the 5-bromo products **5** or **6**. However they may be observed using n.m.r. spectroscopy. Upon addition of bromine to $D_2O$ solutions of **1**($R^1$ = H or Me), and **2**($R^1$ = $R^2$ = Me) signals appropriate to **4** are observed. The 5-proton appears as a complex multiplet centered at δ 4.4 and the 4,6-protons as a multiplet at δ 5.0 with relative integrated intensities of approximately 1:2. The *N*-methyl protons, if present, appear at δ 2.88. Repeat experiments using substrates having deuterium at the 5-position give spectra lacking the absorptions at δ 4.4 and showing much simplification of the multiplet at δ 5.0. The complexity of the

TABLE 1. Variation of the rate of appearance of the brominated product **5** with acidity for the substrates **10** at 30 °C

| $R^1$ | $R^2$ | $X^-$ | $[H_2SO_4]$ ($M$) | $[H_3O^+]$* ($M$) | $k_{obs} \times 10^4$† ($min^{-1}$) |
|---|---|---|---|---|---|
| H | H | $Cl^-$ | 0.250 | 0.261 | 1.88 |
| | | | 0.300 | 0.311 | 2.19 |
| | | | 0.400 | 0.411 | 3.19 |
| | | | 0.500 | 0.511 | 4.12 |
| Me | H | $Cl^-$ | 0.250 | 0.261 | 6.10 |
| | | | 0.350 | 0.361 | 7.95 |
| | | | 0.400 | 0.411 | 9.5 |
| | | | 0.500 | 0.511 | 12.0 |
| Me | Me | $HSO_4^-$‡ | 0.050 | 0.059 | 5.91 |
| | | | 0.100 | 0.110 | 10.8 |
| | | | 0.250 | 0.261 | 28.3 |
| | | | 0.300 | 0.311 | 34.1 |
| | | | 0.430 | 0.441 | 53.3 |
| | | | 0.500 | 0.511 | 63.3 |
| | | | 0.665 | 0.677 | 80.6 |
| | | | 0.690 | 0.702 | 84.0§ |
| | | | 0.500 | 0.511 | 34.5‖ |
| | | | 0.75 | — | 72.6‖ |
| | | | 1.00 | — | 97.1‖ |

*Calculated from the molarity of $H_2SO_4$ assuming the second dissociation constant of $H_2SO_4$ is $K_2 = 1.2 \times 10^{-2}$ (12).
†Average from two or more determinations. Estimated errors are less than 5%.
‡Data for this compound are shown in Fig. 1.
§Single run.
‖At 25 °C.

multiplets and the *N*-methyl absorptions suggest that the species **4** may be present in more than one diastereomeric form.

With time the n.m.r. absorptions we assign to **4** decrease, and are replaced by those appropriate to the 5-bromo derivatives **5** and **6**. These also react with bromine to give materials with no significant u.v. absorptions and which are presumably the 5,5-dibromo-4,6-dihydroxyhexahydropyrimidines **7**. Indeed for **7**($R^1 = R^2$ = Me) a white crystalline material was isolated whose elemental analysis, n.m.r., and mass spectra are consistent with the proposed structure. The n.m.r. (in DMSO-$d_6$) shows two singlets: δ 2.87, area 3 (*N*—Me); δ 5.00, area 1 ($C_{4,6}$—H). The mass spectrum has three peaks at *m/e* 316, 318, 320 (approximate ratio 1:2:1) as expected for **7**($R^1 = R^2$ = Me) having two bromines.

The bromination of the title compounds seems, then, to involve a rapid reaction with bromine to give adducts **4** which slowly undergo elimination to yield the 5-bromo derivatives **5** and **6**. The kinetics of this latter process were measured spectrophotometrically by monitoring the u.v. absorption of the products as a function of time. At fixed acid concentrations, first-order kinetics were observed for all three substrates and the rate constants presented in Table 1 were obtained. Part of these data are shown in Fig. 1. Clearly the process being followed is acid catalyzed, as would be expected for the dehydration **4** ⇄ **8** → **9** ⇄ **5** (see Appendix). The presence of *N*-methyl groups facilitates the reaction, presumably by increasing the proportion of **8** relative to **4**.

Kinetics were also measured in stronger acid (1.0–2.19 $M$ $H_2SO_4$) for **2**($R^1 = R^2$ = Me, $HSO_4^-$) but a minor complication arises in this region in that first-order plots for the increase of product absorbance are significantly curved (10). This we believe to be due to the formation of some **7**($R^1 = R^2$ = Me) which in a very slow process reverts to **5**($R^1 = R^2$ = Me) and so precludes accurate measurement of $A_\infty$.

As the acidity of the medium increases, the proportion of the pseudo-base **3** relative to the cation **2** is decreased (3, 4). Consequently at the higher acid concentrations it is observed that the time for the initial rapid disappearance of bromine is perceptibly longer, since the conversion **2** → **4** is retarded. At the same time, however, the increased acidity facilitates the process **4** → **5**, and at higher acidities it is quite possible

TABLE 2. Variation of rate of appearance of the brominated product **5**($R^1 = R^2 = Me$) with the acidity function $H_0$ for the substrate **10**($R^1 = R^2 = Me$; $X = HSO_4$) at 30 °C

| $[H_2SO_4]$ ($M$) | $H_0$ | $k_{obs} \times 10^2$* ($min^{-1}$) | $\log k_{obs}$† |
|---|---|---|---|
| 1.00 | −0.30 | 1.75 | −1.7570 |
| 1.28 | −0.48 | 2.66 | −1.5751 |
| 1.50 | −0.61 | 3.68 | −1.4342 |
| 2.00 | −0.89 | 5.96 | −1.2248 |
| 2.19 | −0.99 | 8.47 | −1.0721 |

*Average of two or more determinations. Estimated errors less than 5%.
†These values are plotted against $H_0$ in Fig. 2.

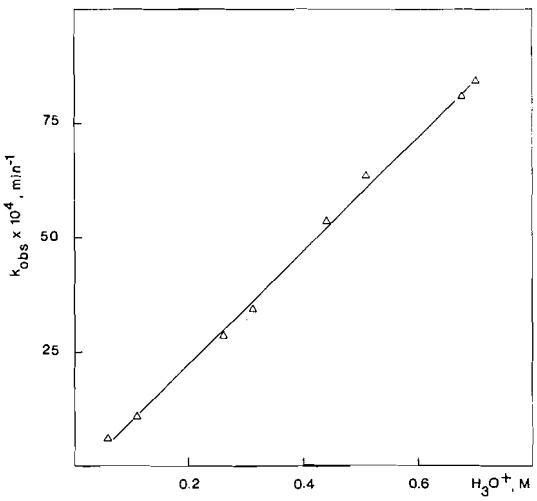



FIG. 1. Variation of the rate of appearance of the product **5**($R^1 = R^2 = Me$) with acidity (30 °C).

that **2** (through **3**) and **5** (through **9**) may compete for bromine and that some of **5** be converted to the dibromo product **7**. This would explain why the $A_\infty$ measured is less than anticipated but does not explain the curvature we have observed. The absorbance measured after 10 half-lives ($A_\infty$) did not remain constant but gradually increased well after the reaction should have theoretically gone to completion if it was strictly limited to the conversion **4** → **5**. This observation suggests a further slow formation of the 5-bromo product **5**. In a separate experiment it was noted that when the 5,5-dibromo adduct **7** was dissolved in 2 $M$ $H_2SO_4$ solution absorption appropriate to **5** appeared very gradually over an extended period of time.

It seems likely, therefore, that the inaccurate value of $A_\infty$, which leads to the curvature of the first-order plots, is due to a slow conversion of **7** to **5**. Although this reaction does not occur significantly during the normal time of measurement of absorbance values, it influences the final absorbance value to a small extent. Hence on lowering $A_\infty$ slightly to correct for this reaction, good straight first-order plots were obtained for the rate of appearance of **5**. Values of $A_\infty$ were chosen to give the best least squares fit of the absorbance data to a first-order plot. Rate constants derived from such plots are shown in Table 2, and they exhibit a linear dependence upon acidity as anticipated (see Fig. 2).

Experiments were also carried out in which the initial bromine concentration was more than twice that of the pyrimidine substrate. Under these conditions one cannot directly observe the appearance of **5** since it reacts rapidly with bromine to give **7** (via **9**). However, following the rapid consumption of 1 mol equiv. of bromine during the formation of **4**, one can

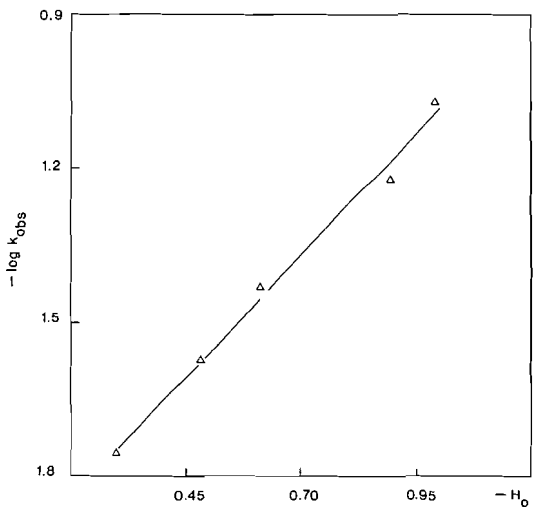



FIG. 2. Variation of the rate of appearance of the product **5**($R^1 = R^2 = Me$) with the acidity function $H_0$ (30 °C).

observe a slow decrease in bromine absorbance as the remaining bromine is consumed by **5** as rapidly as the latter is formed. Consistent with this interpretation, rate constants obtained by measuring the decreasing bromine absorption are, within experimental error, identical to those measured for the appearance of **5** in the absence of excess bromine.[2]

In the dehydration of the intermediate **4** it is envisaged that the slow step is the removal of the proton at the 5-position of **8**. To test this hypothesis 5-deuterio-**2** ($R^1 = R^2 = Me$, $HSO_4^-$) was prepared by isotopic exchange (3, 4), and the rate of its bromination was measured. In 0.5 *M* $H_2SO_4$ it gave $k_{obs} = 10.8 \times 10^{-4}$ $min^{-1}$ from which $k_{obs}^H/k_{obs}^D = 5.9$. Such a large isotope effect is entirely consistent with the rate-determining rupture of $C_5$—H bond of the intermediate **8** (11).[3]

Work in progress also implicates covalent adducts similar to **4** in the bromination of other pyrimidine substrates.

## Experimental

The melting points given below are uncorrected. Ultraviolet determinations were made on a Cary 14 instrument, n.m.r. spectra were obtained from a Varian A-60 spectrometer, and the mass spectrum was run on a Perkin-Elmer-Hitachi RMU-6E mass spectrometer. Elemental analyses were performed by Galbraith Labs. Inc., Knoxville, Tennessee, and by A. B. Gygli, Toronto, Ontario.

*2-Pyrimidinone Hydrochloride (**10**, $R^1 = R^2 = H$; $X = Cl$)*

This compound from Aldrich was recrystallized from ethanol–water before use.

*1-Methyl-2-pyrimidinone Hydrochloride (**10**, $R^1 = Me$; $R^2 = H$; $X = Cl$)*

This compound was prepared by literature methods (4, 13).

*1,2-Dihydro-1,3-dimethyl-2-oxopyrimidinium Hydrogen Sulfate (**10**, $R^1 = R^2 = Me$; $X = HSO_4$)*

Previously (4) this compound was made from the corresponding chloride by treatment with silver sulfate. It is more conveniently made by direct condensation.

1,3-Dimethylurea (8.8 g, 0.1 mol) in 40 ml absolute ethanol was added to 1,1,3,3-tetraethoxypropane (22 g, 0.1 mol) and the resulting solution was cooled in ice water. Upon dropwise addition of 95% sulfuric acid (20 g, 0.2 mol) the stirred solution became yellow and deposited an orange-yellow precipitate. The mixture was then heated at 50° for 30 min. Cooling to room temperature and filtration gave 21 g (95%) of pale yellow crystals. Recrystallization from ethanol–methanol–water afforded 18.3 g (83%) long colorless needles, m.p. 204–206°, reported (4) m.p. 200–205°. The n.m.r. spectrum agreed with literature values (4).

Anal. Calcd. for $C_6H_{10}N_2O_5S$: C, 32.43; H, 4.54; N, 12.61. Found: C, 32.54; H, 4.59; N, 12.72.

The 5-deuterated material was prepared by heating a sealed glass tube containing 2.2 g (0.01 mol) of the above crystals in 10 ml deuterium oxide at 100° for 10 days. The tube was cooled to 0°, opened, and the contents were decolorized by filtration through "Norite". Solvent removal and recrystallization from ethanol–water gave 1.82 g (81%) of long colorless needles. The n.m.r. spectrum in $D_2O$ showed less than 3% protium at the 5-position of the pyrimidine ring.

*5-Bromo-2-pyrimidinone (**6**, $R^1 = H$)*

This was made in 84% yield by the method of Crosby and Berthold (14) but using 2-pyrimidinone hydrochloride in place of the free base.

*5-Bromo-1-methyl-2-pyrimidinone (**6**, $R^1 = Me$)*

To 1-methyl-2-pyrimidinone hydrochloride (0.5 g, 3.4 mmol) in 5 ml water was added saturated bromine water until color persisted. Removal of the solvent under reduced pressure gave a yellow material, which was recrystallized from ethanol to give white flakes, m.p. 237–239° (darkens at 180°), reported (15) m.p. 210–211° (darkens at 170°); n.m.r. ($D_2O$), δ 3.97 (s, 3, $CH_3$), 9.49 and 9.33 (AB "quartet" $J_{4,6} = 3$ Hz, 1 and 1, $H_4$ and $H_6$).

Anal. Calcd. for $C_5H_5N_2OBr$: C, 31.78; H, 2.65; N, 14.83; Br, 42.28. Found: C, 31.80; H, 2.75; N, 14.85; Br, 42.17.

*5-Bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium Bromide (**5**, $R^1 = R^2 = Me$; anion = $Br^-$)*

To 1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium chloride (4) or sulfate (1 mmol) was added 10 ml of 0.1 *M* bromine water. The resulting solution was reduced to dryness, and the pale yellow residue was recrystallized from ethanol to give 0.189 g (67%) bright yellow crystals, m.p. 267–268° (dec); n.m.r. ($D_2O$), δ 3.88 (s, 6, $N_{1,3}$—$CH_3$), 9.05 (s, 2, $H_{4,6}$); u.v. spectrum (9.5% $H_2SO_4$), $\lambda_{max}$ (log ε) 222 (4.10), 346 (3.85).

Anal. Calcd. for $C_6H_8N_2OBr_2$: C, 25.38; H, 2.84; N, 9.87; Br, 56.28. Found: C, 25.59; H, 2.82; N, 9.76; Br, 56.06.

*5,5-Dibromo-4,6-dihydroxy-1,3-dimethylhexahydro-2-oxopyrimidine (**7**, $R^1 = R^2 = Me$)*

To 1 g (3.5 mmol) of the product of the previous preparation was added saturated bromine water until color persisted. A white material (0.97 g, 87%) immediately precipitated from solution, m.p. 135° (dec); n.m.r. (DMSO-$d_6$), δ 2.87 (s, 6, $N_{1,3}$—$CH_3$), 5.00 (s, 2, $H_{4,6}$), 3.40 (broad, 2, $O_{4,6}$—H); mass spectrum *m/e*, 316, 318, 320 (approximate ratio 1:2:1).

Anal. Calcd. for $C_6H_{10}N_2O_3Br_2$: C, 22.67; H, 3.15;

[2]For example, in 0.5 *M* $H_2SO_4$ at 25 °C the rate constant obtained by monitoring product increase in the absence of excess bromine was $3.45 \times 10^{-3}$ $min^{-1}$ (average of 10 runs). That obtained by monitoring bromine decrease was $3.62 \times 10^{-3}$ $min^{-1}$ (average of three runs), when initial bromine exceeded that of pyrimidine substrate.

[3]It should be noted that of the species **1**–**9** and **13** only **8** and **13** have not been directly observed.

TABLE 3. Ultraviolet spectral data and protonation p$K_a$'s of the pyrimidine substrates and their 5-bromo derivatives

| Pyrimidine | p$K_a$ | p$H$ or $H_0$ | $\lambda_{max}$ (log ε) | | Reference |
|---|---|---|---|---|---|
| 2-Pyrimidinone | 2.24 | 6.21 | 298(3.67) | 215(>4.0) | 19 |
| | | 0 | 309(3.75) | 215(>3.2) | |
| 1-Methyl-2-pyrimidinone | 2.5 | 6.0 | 302(3.73) | 215(4.0) | 19 |
| | | 0.3 | 313(3.85) | 215(3.80) | |
| 1,2-Dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrogen sulfate | 7.03* | 10.1 | 296(2.70) | 239(3.93) | 4† |
| | | 0.29 | 316(3.93) | 215(>4.0) | |
| 5-Bromo-2-pyrimidinone | 0.44 | 4.0 | 322(3.54) | 222(4.16) | 20 |
| | | 0.22 | 343(3.65) | 222(4.19) | |
| 5-Bromo-1-methyl-2-pyrimidinone | 0.55 | 4.0 | 326(3.43) | 225(4.0) | 20 |
| | | −2.0 | 346(3.55) | 224(3.96) | |
| 5-Bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium bromide | 3.08‡ | 0.29 | 346(3.85) | 222(4.10) | 6† |
| | | 9.18 | 252(3.88) | <200(>4.00) | |

*For the equilibrium 2 ⇄ 3, $K = [3][H^+]/[2] = 10^{-7.03}$ (4).
†This work.
‡For the equilibrium 5 ⇄ 9, $K = [9][H^+]/[5]$.

N, 8.81; Br, 50.27. Found: C, 22.63; H, 3.05; N, 8.86; Br, 50.13.

*Kinetic Procedures (10)*

Sulfuric acid and sodium thiosulfate solutions were prepared from commercial standard volumetric concentrates. Solutions of bromine in aqueous sulfuric acid were estimated by titration against sodium thiosulfate. This must be done frequently since bromine loss to the air is considerable.

The concentration of hydronium ion in dilute acid solutions was calculated assuming the second dissociation constant of sulfuric acid to be $1.2 \times 10^{-2}$ (12). For stronger acid solutions values of $H_0$ were obtained from Johnson *et al.* (16) using "wt % $H_2SO_4$" calculated from "molarity" and the known density of sulfuric acid – water mixtures (17).

Rates of product formation were measured by monitoring a suitable wavelength in the region 365–375 nm using a Cary 14 spectrophotometer. Temperature control was maintained by circulating water through the cell holders from a Neslab TE9 constant temperature bath kept at 30.00 ± 0.02 °C. Solutions were kept at 30 °C prior to mixing and the start of kinetic measurements. Normally (>15) absorbance values were measured over at least 2 half-lives, and $A_\infty$ values measured after at least 10 half-lives. Plots of ln $(A_\infty - A)$ *vs.* time gave good straight lines but only those having correlation coefficients >0.9998 were used to calculate rate constants. Such rate constants were independent of the initial concentrations of either bromine or pyrimidine substrates.

The rate data for the 5-deuterio substrate show initial curvature due to the preferential consumption of the small amount of protio material (<3%). Rate constants were obtained by the method of Brown and Fletcher (18) which utilizes the latter portions of the rate data which are very linear. The initial curvature corresponded to <3% protio material in agreement with the estimate from n.m.r. spectra. The rate constant for 5-deuterio substrate given in the text is the average of three determinations (1.05, 1.08, and $1.10 \times 10^{-3}$ min$^{-1}$).

Ultraviolet spectral data for the pyrimidine substrates and their 5-bromo derivatives are presented in Table 3.

## Appendix[4]

It is proposed that rates we have measured are for the reaction

$$4 + H^+ \overset{K}{\rightleftharpoons} 8 \underset{\text{slow}}{\overset{k}{\longrightarrow}} 9 \rightleftharpoons 5$$

For this scheme rate $= k_{obs}[5] = k[8]$, since $[5] \gg [9]$. However, the rate of appearance of **5** must equal the rate of the stoichiometric disappearance of **4**, and thus

$$\text{rate} = k_{obs}[4]_{st} = k[8],$$

and

$$k_{obs} = k[8]/[4]_{st}$$

where $[4]_{st} = ([4] + [8])$

For the equilibrium between **4** and **8**,

$$K = \frac{[4][H^+]}{[8]},$$

and so

$$\frac{[8]}{([4] + [8])} = \frac{[H^+]}{(K + [H^+])}$$

Therefore,

$$k_{obs} = \frac{k[H^+]}{(K + [H^+])}$$

a familiar result.

Also as long as the equilibrium lies in favor of **4**, *i.e.* $K \gg [H^+]$, then

$$k_{obs} = k[H^+]/K$$

and acid catalysis should be observed.

[4]The development of these equations was requested by a referee.

Our results require, therefore, that even in the strongest acid (2 *M* $H_2SO_4$), that **4** predominates over **8**. One might expect that the equilibrium formation of an iminium ion from a carbinolamine would be relatively complete in such a medium. In the present case, however, the iminium system of **8** is conjugated to a carbonyl and its equilibrium formation should be less facile. Furthermore, the observation of **4** (by n.m.r.), but not **8**, in solutions of 1–2 *M* acid is consistent with a value of $K \gg 1$.

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