4172 *J. Org. Chem.* **1981**, *46*, 4172-4178

# Covalent Hydration in 4-Pyrimidinones. Detection through Kinetics of Bromination in Aqueous Acidic Solution

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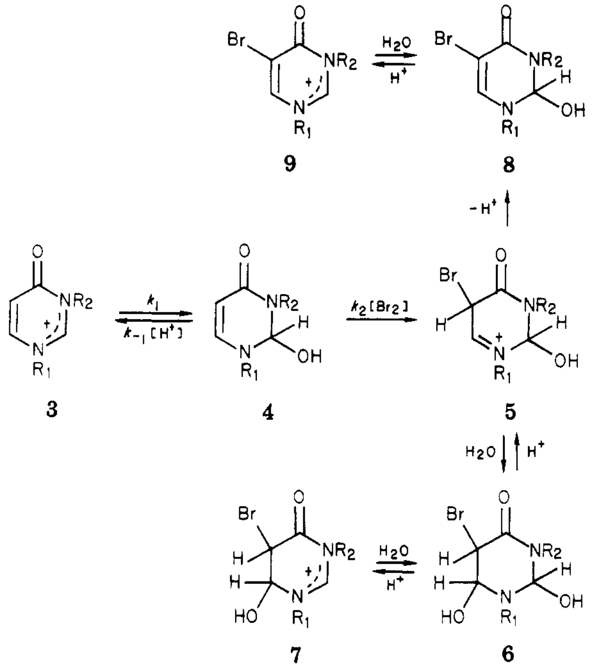
*Received January 26, 1981*

The kinetics of the fast disappearance of bromine due to reaction with 4(3*H*)-pyrimidinone (**1a**) and with three *N*-methyl derivatives (**2b**, **1c**, **3d**) in aqueous solutions of pH 0-5 have been measured by the stopped-flow method. The data are consistent with attack of bromine upon a covalent hydrate (or pseudobase), **4**, of the substrate, with the rate-determining step depending upon the acidity. At high acidity (pH <2) bromine attack upon **4** is rate limiting, whereas at low acidity (pH >3) formation of **4** from the appropriate cation **3** is rate limiting. The present results, combined with those of an earlier study,[7] show that bromination of 4-pyrimidinones in acidic aqueous solution involves a complex addition-elimination sequence (Scheme I). Furthermore, it is estimated that **1a** at equilibrium in aqueous solution exists as the covalent hydrate **4a** to the extent of only $\sim 3 \times 10^{-4}$%. The results emphasize the dramatic effect that covalent hydration may have upon the reactivity of heterocyclic systems.

Covalent hydration of electron-deficient nitrogen heterocycles has been extensively studied, most notably by Albert and co-workers.[1] For the most part it has been detected by its effect upon acid-base equilibria and upon spectra.[1] However, covalent hydrates may be important reaction intermediates even when in concentrations so small as to be undetectable by normal means. For example, they may be intermediates in the enzymatic deaminations (hydrolyses) of adenosine, cytosine, and their nucleosides.[2a,b] They are also plausible intermediates in the oxidation of various heterocycles catalyzed by xanthine oxidase.[2c-f] Covalent hydration also affects the photophysics of the important ligands 2,2′-bipyridine and 1,10-phenanthroline.[3a] Furthermore, some complexes containing these ligands capture water.[3b] The intermediacy of covalent hydrates has also been invoked to explain unusual reactivity observed in the H-D exchange reaction of certain heterocycles in acidic deuterium oxide.[4]

For the most part covalent hydration has been observed in bicyclic (or larger) heterocycles containing two or more aza nitrogens.[1] It is normally only apparent in monocyclic systems which contain three strongly electron-withdrawing groups (2-aza nitrogens plus nitro, 3-aza nitrogens, etc.).[1] However, the present study, together with some earlier work,[5a] shows that it can have dramatic effects upon the reactivity of simple pyrimidinones.

Scheme I[a]



[a] **a**, $R_1 = R_2 = H$; **b**, $R_1 = Me$, $R_2 = H$; **c**, $R_1 = H$, $R_2 = Me$; **d**, $R_1 = R_2 = Me$.

In previous studies we have shown that the bromination of 2(1*H*)-pyrimidinone in acidic aqueous solution involves a multistep addition-elimination sequence involving covalent hydrates.[5] More specifically, there is initially fast attack by bromine upon the covalent hydrate of 2(1*H*)-pyrimidinone[5a] leading to the formation of an observable addition intermediate which undergoes slow dehydration to 5-bromo-2(1*H*)-pyrimidinone.[5c,d] This product also reacts with bromine by way of the covalent hydrate,[5e] giving a 5,5-dibromo derivative.[5d] In another study we showed that bromination of 4(3*H*)-quinazolinone in aquous acid involves attack of bromine upon the benzenoid ring of a covalent hydrate of the substrate.[6]

Our initial study[7] of 4(3*H*)-pyrimidinone (**1a**) and its *N*-methyl derivatives showed that they react with bromine in aqueous acid to give observable intermediates **7** (Scheme I). Moreover, since these intermediates are cationic, their

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[1] (a) Albert, A.; Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1965**, *4*, 1-42. (b) Perrin, D. D. *Ibid.* **1965**, *4*, 43-73. (c) Albert, A. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 919-928. (d) Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117-143.

[2] (a) Wolfenden, R. In "Transition States in Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1979, Chapter 15. (b) Wolfenden, R. *Acc. Chem. Res.* **1972**, 5, 10-18. (c) Hamilton, G. A. *Prog. Bioorg. Chem.* **1971**, *1*, 83-157. (d) Bergmann, F.; Kwietny, H.; Levin, G.; Brown, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 598-605. (e) Bergmann, F.; Kwietny, H. *Biochim. Biophys. Acta* **1959**, *33*, 29-46. (f) We note that both 2-pyrimidinone and 4-pyrimidinone are readily oxidized by xanthine oxidase and aldehyde oxidase. Krenitsky, T. A.; Neil, S. M.; Elion, G. B.; Hitchings, G. H. *Arch. Biochim. Biophys.* **1972**, *150*, 585-599.

[3] Henry, M. S.; Hoffman, M. Z. *J. Am. Chem. Soc.* **1977**, *99*, 5201-5203; *J. Phys. Chem.* **1979**, *83*, 618-625. (b) Bielli, E.; Gillard, R. D.; James, D. W. *J. Chem. Soc., Dalton Trans.* **1976**, 1837-1842 and references therein.

[4] (a) Katritzky, A. R.; Kingsland, M.; Tee, O. S. *Chem. Commun.* **1968**, 289-290; *J. Chem. Soc. B* **1968**, 1484-1491. (b) Katritzky, A. R.; Pojarlieff, I. *J. Chem. Soc. B* **1968**, 873-877. (c) Bressel, U.; Katritzky, A. R.; Lea, J. R. *Ibid.* **1971**, 4-10.

[5] (a) Tee, O. S.; Paventi, M. *J. Org. Chem.* **1980**, *45*, 2072-2076. (b) Tee, O. S.; Thackray, D. C.; Berks, C. G. *Can. J. Chem.* **1978**, *56*, 2970-2976. (c) Tee, O. S., Banerjee, S. *J. Chem. Soc., Chem. Commun.* **1972**, 1032-1033. (d) Tee, O. S.; Banerjee, S. *Can. J. Chem.* **1974**, *52*, 451-457. (e) Banerjee, S.; Tee, O. S.; Wood, K. D. *J. Org. Chem.* **1977**, *42*, 3670-3673.

[6] Tee, O. S.; Patil, G. V. *J. Org. Chem.* **1976**, *41*, 838-845.

[7] Tee, O. S.; Banerjee, S. *J. Org. Chem.* **1979**, *44*, 3256-3261.

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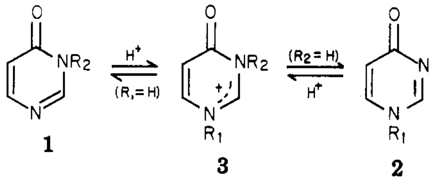
dehydration (7 ⟶ 9) shows unusual acidity dependence[7] By using the stopped-flow method we have now been able to obtain kinetic information about the processes leading to the formation of the intermediates **7**. The results described in the present paper are fully consistent with 4-(3*H*)-pyrimidinone (**1a**) reacting with bromine via its covalent hydrate **4a** (Scheme I) as postulated earlier.[7] Likewise, the methyl derivatives **2b** and **1c** react via covalent hydrates **4b,c** and the quaternary dimethyl cation **3d** by way of its pseudobase **4d**.

## Results and Discussion

The substrates used in the present study were 4(3*H*)-pyrimidinone (**1a**), 1-methyl-4-pyrimidinone (**2b**), 3-methyl-4-pyrimidinone (**1c**), and the perchlorate salt of the 1,4-dihydro-1,3-dimethyl-4-oxopyrimidinium cation



a, $R_1 = R_2 = H$; b, $R_1 = Me$, $R_2 = H$; c, $R_1 = H$, $R_2 = Me$; d, $R_1 = R_2 = Me$

(**3d**). The monomethyl derivatives (**1c** and **2b**) were chosen as models for the principal tautomers (**1a** and **2a**) of "4-hydroxypyrimidine",[8] and the dimethyl cation **3d** was chosen as a model for their protonated forms.[9]

The disappearance of bromine due to reaction with an excess of the above four substrates in aqueous solutions of pH 0–5 was monitored by UV spectrophotometry and the stopped-flow technique. The observed kinetic order varies with acidity in the same way as observed in our recent studies of 2-pyrimidinones,[5a,b] viz., pseudo first order at pH <2, pseudo zero order at pH >3.5, and a mixed-order in the intermediate range pH 2–3.5. This behavior we attribute to bromine attacking the covalent hydrate (or pseudobase)[10] **4** formed from the cation **3** (eq 1 and Scheme I). Assuming a steady-state concentration of **4**, the mechanism of eq 1 requires the rate law shown in eq 2.[5b,12]

$$H_2O + 3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H^+ + 4 \xrightarrow[Br_2]{k_2} 5 \qquad (1)$$

$$\text{rate} = \frac{k_1k_2[3][Br_2]}{k_{-1}[H^+] + k_2[Br_2]} \qquad (2)$$

The behavior observed for bromination of the dimethyl cation **3d** is fully accounted for by eq 2. Moreover, a kinetic study of the formation of the pseudobase **4d** from **3d** (and the reverse reaction) gave values of $k_1$ and $k_{-1}$ compatible with those obtained from the bromination kinetics. These values, together with a value of $k_2$ from the bromination study, justify the assumption of a steady-state concentration of the pseudobase **4d** in deriving eq 2.

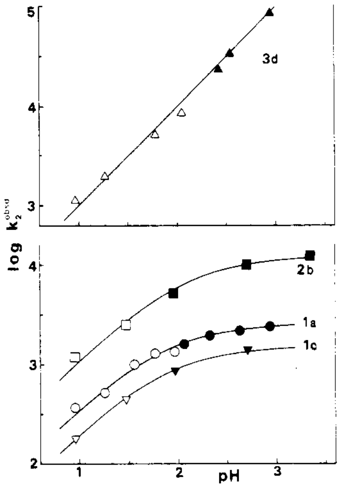


**Figure 1.** pH dependence of second-order rate constants for the reaction of bromine with **1a**, **2b**, **1c**, and **3d**. The significance of the open and closed symbols is explained in the text.

The rate law in eq 2 also acounts for the behavior of the other substrates (**1a**, **2b**, **1c**) when allowance is made for the fraction of these existing in their protonated froms (**3a–c**)[9] at the various pHs employed. To do this one substitutes for [3] in eq 2 using eq 3. In this equation,

$$[3] = [S]_s[H^+]/(K_1 + [H^+]) \qquad (3)$$

$[S]_s$ is the stoichiometric concentration of the substrate, and $K_1$ is the acid dissociation constant of its conjugate acid **3** (**a**, **b**, or **c**).

**pH 0–2.** Results for this region are shown in Table I. At a given pH, and in the presence of an excess of substrate, bromine disappearance afforded pseudo-first-order rate constants ($k_1^{obsd}$) which vary linearly with substrate concentration (see Table I). Some kinetic runs which were carried out with the substrate not in large excess were analyzed directly for second-order behavior. Values of $k_2^{obsd}$ obtained from such analysis are denoted by a superscript *e* in Table I. Altogether our data in this region of pH are consistent with the rate law expressed by eq 4,

$$\text{rate} = k_1^{obsd}[Br_2]_s = k_2^{obsd}[S][Br_2] \qquad (4)$$

where $k_2^{obsd}$ is the second-order rate constant corrected for the difference $[Br_2]_s$ and $[Br_2]$ due to tribromide ion formation.[5a,b,6] Values of $k_2^{obsd}$ for all four substrates in the region pH 1–2 are plotted as open symbols in Figure 1.[13]

For the dimethyl cation **3d** the pH dependence of $k_2^{obsd}$ is explicable by equating eq 2 and 4 and imposing the inequality $k_{-1}[H^+] \gg k_2[Br_2]$. In this case eq 5 holds,[5b]

$$k_2^{obsd} = k_1k_2/k_{-1}[H^+] = k_2K_{R^+}/[H^+] \qquad (5)$$

where $K_{R^+}$ is the formation constant for the pseudobase[11] **4d**. The straight line drawn for **3d** in Figure 1 assumes $k_2K_{R^+} = 97.5\ s^{-1}$. Since $pK_{R^+} = 7.53$,[7] $K_{R^+} = 2.95 \times 10^{-8}$ M, and so $k_2 = 3.3 \times 10^9\ M^{-1}\ s^{-1}$.

The data for the other substrates (**1a**, **2b**, **1c**) show similar behavior (Figure 1)[13] but with a tendency to level as pH approaches their protonation p*K*s.[9] Since in this region of pH the substrates are largely protonated (as

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[8] (a) Mason, S. F. *J. Chem. Soc.* **1958**, 674–685. (b) Beak, P.; Fry, F. S.; Lee, J.; Steele, F. *J. Am. Chem. Soc.* **1976**, *98*, 171–179.

[9] Brown, D. J.; Hoerger, E.; Mason, S. F. *J. Chem. Soc.* **1955**, 211–217.

[10] The term "covalent hydrate" applies to **4a–c** which result from the formal addition of water to **1a**, **2b**, and **1c**. The term "pseudobase" applies to **4d** which results from the formal capture of hydroxide ion by the quaternary dimethyl cation **3d**. For further amplification see ref 1 and 11, respectively.

[11] Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1–82.

[12] A similar rate law pertains to the iodination of 1,3-dimethyl-2-indolinone in basic solution: Challis, B. C.; Rzepa, H. S. *J. Chem. Soc., Perkin Trans 2* **1975**, 1822–1826.

[13] In the interests of clarity these plots do not contain the data for $[Br^-] \simeq 1.1$ M. Since the ionic strength for these measurements is much higher than for the rest, they do not form a continuous set of data with that depicted in Figure 1. Such discontinuity was not particularly apparent in our earlier work,[5a] presumably due to a fortuitous cancellation of ionic strength effects upon $K_{R^+}$ and $k_2$ (see eq 5). Note, however, that the data obtained at high $\mu$ ($\sim$1.1 M) do show that same order of reactivity and dependence on pH as shown in Figure 1.

Table I. Second-Order Rate Constants for the Reaction of Bromine with 4-Pyrimidinones[a]

| substrate (S) | $[Br^-]$,[b] M | pH[c] | $10^3[S]$, M | $k_1^{obsd}$, $s^{-1}$ | $10^{-2}k_2^{obsd}$,[d] $M^{-1}\,s^{-1}$ |
|---|---|---|---|---|---|
| **1a** | 1.100 | −0.035 | 2.0 | 0.0121 | 1.30 |
| | 1.144 | 0.264 | 2.0 | 0.0171 | 1.90 |
| | 1.088 | 0.614 | 2.0 | 0.0304 | 3.22 |
| | 1.098 | 0.908 | 2.0 | 0.0491 | 5.24 |
| | 1.097 | 1.22 | 2.0 | 0.0834 | 8.89 |
| | 0.11 | 0.96 | 0.2 | | 4.68[e] |
| | | | 0.4 | | 4.55[e] |
| | | | 0.75 | | 4.63[e] |
| | | | 1.0 | | 4.53[e] |
| | 0.1 | 1.26 | 0.5 | 0.0868 | 5.41 |
| | | | 0.75 | 0.123 | 4.93 |
| | 0.105 | 1.56 | 2.0 | 0.648 | 9.93 |
| | 0.109 | 1.78 | 2.0 | 0.858 | 13.1 |
| | | | 4.0 | 1.92 | 14.6 |
| | 0.1 | 1.98 | 2.0 | 0.973 | 14.0 |
| | 0.1 | 2.06 | 2.0 | 1.07[f] | 15.5 |
| | 0.1 | 2.34 | 1.5 | 1.02[f] | 19.8 |
| | | | 2.0 | 1.31[f] | 18.8 |
| | 0.1 | 2.64 | 2.0 | 1.50[f] | 21.6 |
| | 0.1 | 2.95 | 1.5 | 1.28[f] | 24.7 |
| | | | 2.0 | 1.62[f] | 23.3 |
| **2b** | 1.100 | −0.035 | 2.0 | 0.0301 | 3.21 |
| | 1.144 | 0.264 | 2.0 | 0.0416 | 4.61 |
| | 1.088 | 0.614 | 2.0 | 0.0779 | 8.23 |
| | 1.098 | 0.908 | 2.0 | 0.140 | 14.9 |
| | 1.097 | 1.22 | 2.0 | 0.249 | 26.6 |
| | 0.11 | 0.96 | 0.5 | 0.195 | 12.9 |
| | | | 0.75 | 0.278 | 11.8 |
| | | | 1.0 | 0.378 | 11.9 |
| | | | 1.5 | 0.583 | 12.0 |
| | | | 2.0 | 0.780 | 11.9 |
| | 0.111 | 1.48 | 1.0 | 0.818 | 25.7 |
| | | | 2.0 | 1.62 | 24.8 |
| | 0.1 | 1.98 | 1.0 | 1.77[f] | 52.3 |
| | | | 2.0 | 3.60[f] | 51.8 |
| | 0.1 | 2.71 | 1.0 | 3.43[f] | 101 |
| | 0.1 | 3.36 | 0.5 | 2.11[f] | 132 |
| | | | 1.0 | 3.72[f] | 110 |
| **1c** | 1.100 | −0.035 | 2.0 | 0.00529 | 0.566 |
| | 1.144 | 0.264 | 2.0 | 0.00705 | 0.783 |
| | 1.088 | 0.614 | 2.0 | 0.0134 | 1.43 |
| | 1.098 | 0.908 | 2.0 | 0.0236 | 2.52 |
| | 1.097 | 1.22 | 2.0 | 0.0416 | 4.44 |
| | 0.11 | 0.96 | 0.5 | | 1.84[e] |
| | | | 0.625 | | 1.78[e] |
| | | | 0.75 | | 1.77[e] |
| | | | 1.0 | | 1.80[e] |
| | | | 1.5 | | 1.81[e] |
| | | | 2.0 | | 1.79[e] |
| | 0.111 | 1.48 | 1.0 | 0.144 | 4.52 |
| | | | 2.0 | 0.294 | 4.50 |
| | 0.1 | 1.98 | 1.0 | 0.291[f] | 8.59 |
| | | | 2.0 | 0.532[f] | 7.65 |
| | 0.1 | 2.71 | 0.5 | 0.233[f] | 14.5 |
| | | | 1.0 | 0.491[f] | 14.5 |
| **3d** | 1.100 | −0.035 | 2.0 | 0.0239 | 2.55 |
| | 1.144 | 0.264 | 2.0 | 0.0352 | 3.92 |
| | 1.088 | 0.614 | 2.0 | 0.0617 | 6.52 |
| | 1.098 | 0.908 | 2.0 | 0.111 | 11.9 |
| | 1.097 | 1.22 | 2.0 | 0.206 | 22.0 |
| | 0.11 | 0.96 | 0.5 | 0.168 | 11.1 |
| | | | 1.0 | 0.402 | 12.6 |
| | 0.1 | 1.26 | 0.5 | 0.298 | 18.6 |
| | | | 1.0 | 0.732 | 21.6 |
| | 0.109 | 1.78 | 0.2 | | 51.9[e] |
| | | | 0.4 | | 53.0[e] |
| | 0.1 | 2.05 | 0.2 | | 85.6[e] |
| | | | 0.3 | | 84.7[e] |
| | | | 0.4 | | 88.1[e] |
| | 0.1 | 2.42 | 0.2 | 1.29[f] | 242 |
| | | | 0.4 | 2.83[f] | 227 |
| | 0.1 | 2.54 | 0.5 | 5.30[f] | 330 |
| | | | 1.0 | 10.9[f] | 322 |
| | 0.1 | 2.95 | 0.5 | 13.6[f] | 850 |
| | | | 1.0 | 27.8[f] | 819 |

[a] At 30 °C $[Br_2]_0 = 5 \times 10^{-5}$ M. $\mu = 0.11$ M; except where $[Br^-]$ exceeds this and at pH 1.26 ($\mu = 0.175$ M). [b] $[Br^-]$ = [KBr] + [HBr]. [c] For pH >1.78 buffers were used. Elsewhere pH = −log [HBr], except that pH 1.26 is for 0.05 M $H_2SO_4$. [d] Obtained from $k_1^{obsd}$ by correction for substrate concentration and tribromide ion formation (see Experimental Section) except where noted otherwise. [e] Obtained from direct second-order analysis and corrected for tribromide ion formation. [f] From mixed-order analysis.

**3a–c**),[9] the pH dependence of $k_2^{obsd}$ may be expressed by eq 6,[14] where $K_1$ is as in eq 3 and $K_{R^+} = [4][H^+]/[3]$.

$$k_2^{obsd} = k_1k_2/k_{-1}(K_1 + [H^+]) \qquad (6a)$$

$$= k_2K_{R^+}/(K_1 + [H^+]) \qquad (6b)$$

**pH 2–3.** In this region we observed mixed-order behavior very similar to that for 2(1*H*)-pyrimidinones.[5a,b] As with the earlier work, the results are best interpreted through an analysis based upon the integrated form of eq 3.[15] This analysis is described fully in ref 5a and is similar to that of Challis and Rzepa.[12]

From the first-order component of the data were obtained the $k_1^{obsd}$ values[5a] given in Table I and denoted by a superscript *f*. Values of $k_2^{obsd}$ obtained from these are also in Table I and plotted as solid symbols in Figure 1. They continue the behavior described in the previous section.

The mixed-order data obtained in this region also contain a zero-order component,[5a,b] and so one can also extract zero-order rate constants $k_0^{obsd}$ using the analysis previously described.[5a] Such values are in Table II (denoted by superscript *b*), and since these are dependent upon substrate concentration (eq 7) they have been converted

$$\text{rate} = k_0^{obsd} = k_1^{obsd\prime}[S] \qquad (7)$$

to first-order rate constants $k_1^{obsd\prime}$ which are plotted as solid symbols in Figure 2. The significance of these rate constants is discussed below.

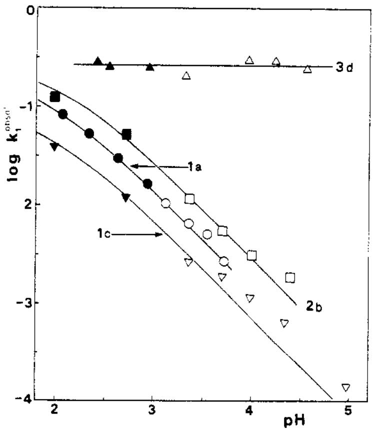

**Figure 2.** pH dependence of first-order rate constants obtained from the reaction of bromine with **1a**, **2b**, **1c**, and **3d**. The significance of the open and closed symbols is explained in the text.

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[14] Obtained by substituting [**3**] from eq 3 into eq 2, invoking $k_{-1}[H^+] \gg k_2[Br_2]$, and setting the result equal to **4** (cf. ref 5a).

[15] See eq 11 and 12 of ref 5a.

Table II. First-Order Rate Constants for the Formation of 4 from 3[a]

| substrate (S) | pH | $10^3$[S], M | $10^5 k_0^{\text{obsd}}$, M $s^{-1}$ | $10^2 k_1^{\text{obsd}'}$, $s^{-1}$ |
|---|---|---|---|---|
| **1a** | 2.06 | 2.0 | 16.1[b] | 8.05 |
|  | 2.34 | 1.5 | 8.1[b] | 5.40 |
|  |  | 2.0 | 10.4[b] | 5.20 |
|  | 2.64 | 2.0 | 6.02[b] | 3.01 |
|  | 2.95 | 1.5 | 2.43[b] | 1.62 |
|  |  | 2.0 | 3.22[b] | 1.61 |
|  | 3.11 | 2.0 | 1.94 | 0.972 |
|  |  | 2.5 | 2.83 | 1.13 |
|  | 3.36 | 1.5 | 0.991 | 0.661 |
|  | 3.55 | 1.5 | 0.797 | 0.531 |
|  |  | 2.0 | 1.03 | 0.513 |
|  | 3.72 | 2.0 | 0.546 | 0.273 |
| **2b** | 1.98 | 1.0 | 12.0[b] | 12.0 |
|  |  | 2.0 | 24.0[b] | 12.0 |
|  | 2.71 | 1.0 | 4.71[b] | 4.71 |
|  | 3.36 | 0.5 | 0.610[b] | 1.22 |
|  |  | 1.0 | 1.21[b] | 1.21 |
|  | 3.70 | 1.0 | 0.561 | 0.561 |
|  | 4.00 | 1.0 | 0.328 | 0.328 |
|  | 4.40 | 1.0 | 0.185 | 0.185 |
|  |  | 2.0 | 0.412 | 0.206 |
| **1c** | 1.98 | 1.0 | 3.45[b] | 3.45 |
|  |  | 2.0 | 7.80[b] | 3.90 |
|  |  | 0.5 | 0.595[b] | 1.19 |
|  |  | 1.0 | 1.13[b] | 1.13 |
|  | 3.36 | 0.5 | 0.130 | 0.260 |
|  |  | 1.0 | 0.270 | 0.270 |
|  | 3.69 | 1.0 | 0.188 | 0.188 |
|  | 3.99 | 1.0 | 0.168 | 0.168 |
|  | 4.34 | 1.0 | 0.0650 | 0.0650 |
|  |  | 2.0 | 0.140 | 0.0700 |
|  | 4.97 | 2.0 | 0.0449 | 0.0225 |
| **3d** | 2.42 | 0.2 | 5.64[b] | 28.2 |
|  |  | 0.4 | 10.8[b] | 26.9 |
|  | 2.54 | 0.5 | 12.2[b] | 24.4 |
|  |  | 1.0 | 25.2[b] | 25.2 |
|  | 2.95 | 0.5 | 12.2[b] | 24.4 |
|  |  | 1.0 | 24.9[b] | 24.9 |
|  | 3.32 | 0.25 | 5.06 | 20.2 |
|  |  | 0.5 | 10.3 | 20.5 |
|  | 3.96 | 0.5 | 15.0 | 30.0 |
|  |  | 1.0 | 30.2 | 30.2 |
|  | 4.23 | 0.3 | 8.52 | 28.4 |
|  | 4.55 | 0.1 | 2.67 | 26.7 |

[a] At 30 °C, [KBr] = 0.1 M, $[Br_2]_0 = 5 \times 10^{-5}$ M, and buffers of 0.01 M, thus $\mu = 0.11$ M. [b] From mixed-order analysis.

**pH 3–5.** In this region the disappearance of bromine in the presence of an excess of substrate exhibits pseudo-zero-order behavior (cf. ref 5a,b), and the zero-order rate constants $k_0^{\text{obsd}}$ vary with substrate concentration in accord with eq 7. Values of $k_0^{\text{obsd}}$ and the derived $k_1^{\text{obsd}'}$ are presented in Table II, and the latter are depicted by open symbols in Figure 2. They continue the same pH dependencies exhibited by the analogous rate constants obtained from mixed-order analysis (solid symbols in Figure 2).

The value of $k_1^{\text{obsd}'}$ for the dimethyl cation **3d** remains essentially constant over the pH range studied, and, we believe, this represents the rate constant for attack of water upon **3d**, leading to the pseudobase **4d**. In terms of eq 2, this situation obtains if $k_{-1}[H^+] \ll k_2[Br_2]$, that is, if reversal of the pseudobase **4d** is much slower than its capture by bromine (eq 1). Equating eq 2 with eq 7 (S = **3d**) with the above inequality imposed leads to $k_1^{\text{obsd}'} = k_1$. On this basis $k_1 = 0.26$ $s^{-1}$, and since $K_{R^+} = k_1/k_{-1} = 2.95 \times 10^{-8}$ M (see eq 5), we have $k_{-1} = 8.8 \times 10^6$ $M^{-1}$ $s^{-1}$. Note that these values of $k_1$ and $k_{-1}$ and the value of $k_2 = 3.3 \times 10^9$ $M^{-1}$ $s^{-1}$ (evaluated above) support the use of the steady-state assumption necessary for the derivation of eq 2.

The acidity dependences shown by the $k_1^{\text{obsd}'}$ values for the other substrates (**1a**, **2b**, **1c**) in Figure 2 are explicable by rate-determining attack of water upon their conjugate acids (**3a–c**), forming the covalent hydrates (**4a–c**). Since the concentrations of **3a–c** vary according to eq 3, application of the same reasoning as in the previous paragraph leads to eq 8. This equation generates curves of the form shown in Figure 2.

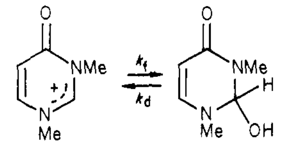
$$k_1^{\text{obsd}'} = k_1[H^+]/(K_1 + [H^+]) \qquad (8)$$

The data for the parent 4(3*H*)-pyrimidinone (**1a**) do not extend above pH 4. Around this pH the order changes to second order, and the appropriate rate constant increases linearly with pH. This we believe results from reaction upon the anion of **1a**.[16] Similar observations have been made for 2(1*H*)-pyrimidinone.[5a,16]

A feature of the data plotted in Figure 2 is the deviations *above* the calculated curve which are evident for the 3-methyl derivative **1c**. These deviations, we believe, are due to the incursion of (succinate) buffer catalysis,[5b] a topic which is addressed in the next section.

In summary, the data for all four substrates over a wide range of pH (0–4 for **1a** and 0–5 for the others) are explicable by the mechanism of eq 1 and its rate law, eq 2, that is, by bromine attack upon the species **4** formed from the cations **3** (Scheme I), with the rate-determining step depending upon the acidity.

**Equilibration Studies.** In order to provide further support for the interpretation given above, we have also studied the kinetics of equilibration[5b,11] of the quaternary cation **3d** and its pseudobase **4d** (eq 9). At a given pH



**3d** **4d** (9)

the observed first-order rate is the sum of rate constants for the formation and decomposition of the pseudobase, i.e., $k_{\text{obsd}} = k_f + k_d$.[11] These rate constants are also related through the equilibrium constant $K_{R^+} = [H^+][\mathbf{4d}]/[\mathbf{3d}]$ according to the eq 10.[11]

$$k_f = k_{\text{obsd}} K_{R^+}/(K_{R^+} + [H^+]) \qquad (10a)$$

$$k_d = k_{\text{obsd}}[H^+]/(K_{R^+} + [H^+]) \qquad (10b)$$

Values of $k_{\text{obsd}}$ obtained over a wide a range as possible are given in Table III along with values of $k_f$ and $k_d$ calculated therefrom using $K_{R^+} = 2.95 \times 10^{-8}$ M ($pK_{R^+} = 7.53$).[7] These rate constants are plotted in Figure 3 (cf. Figure 3 of ref 11). Their pH dependence may be described by eq 11, where $k_1$ and $k_{-1}$ are the same as previously (eq 1), and $k$ and $k_{OH}$ refer to eq 12. The curves

$$k_f = k_1 + k_{OH}[OH^-] \qquad (11a)$$

$$k_d = k + k_{-1}[H^+] \qquad (11b)$$

$$\mathbf{3d} + OH^- \underset{k}{\overset{k_{OH}}{\rightleftharpoons}} \mathbf{4d} \qquad (12)$$

shown in Figure 3 were calculated using $k_1 = 0.2$ $s^{-1}$, $k_{OH} = 1.7 \times 10^7$ $M^{-1}$ $s^{-1}$, $k = 8$ $s^{-1}$, and $k_{-1} = 7 \times 10^6$ $M^{-1}$ $s^{-1}$.

The values of $k_1$ and $k_{-1}$ are in reasonable agreement with the values of $k_1 = 0.26$ $s^{-1}$ and $k_{-1} = 8.8 \times 10^6$ $M^{-1}$ $s^{-1}$ which were obtained from the study of the bromination

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[16] Tee, O. S.; Paventi, M., work in progress.

**Table III. Pseudo-First-Order Rate Constants for the Formation and Decomposition of Pseudobase 4d**[a]

| pH | $k^{obsd}$, $s^{-1}$ | $k_f$, $s^{-1}$ | $k_d$, $s^{-1}$ |
|---|---|---|---|
| 4.72 | 122 | 0.2 | 121.8 |
| 5.02 | 70.6 | 0.2 | 70.4 |
| 5.25 | 43.4 | 0.2 | 43.2 |
| 5.47 | 30.1 | 0.3 | 29.8 |
| 5.69 | 22.6 | 0.3 | 22.3 |
| 6.09 | 14.7 | 0.5 | 14.2 |
| 6.21 | 12.0 | 0.55 | 11.4 |
| 6.60 | 11.7 | 1.53 | 10.5 |
| 6.79 | 11.3 | 1.74 | 9.56 |
| 6.94 | 11.6 | 2.37 | 9.23 |
| 7.11 | 12.2 | 3.36 | 8.84 |
| 7.24 | 14.4 | 4.88 | 9.52 |
| 7.41 | 15.0 | 6.47 | 8.53 |
| 7.64 | 23.3 | 13.1 | 10.2 |
| 7.85 | 42.7 | 28.9 | 13.8 |
| 8.04 | 52.4 | 40.0 | 12.4 |
| 8.18 | 88.6 | 72.4 | 16.2 |
| 8.38 | 128 | 112 | 16.0 |
| 8.60 | 165 | 152 | 13.0 |

[a] At 30 °C, [KBr] = 0.1 M, and $\mu$ = 0.11 M.

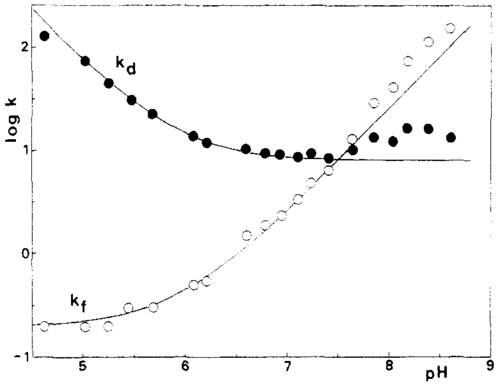


**Figure 3.** pH dependence of the rate constants for the formation ($k_f$) and decomposition ($k_d$) of the pseudobase **4d** (see eq 9).

of **3d** described above. This agreement provides strong support for our interpretation of the kinetics of bromination of **3d**, and, by implication, of the other substrates also.

The deviations from the calculated curves in Figure 3 at pH >7.5 can be attributed to buffer catalysis. There have been indications of such catalysis in work on other cation–pseudobase systems.[5b,11,17,18] More specifically, it is suggested here that formation of the pseudobase **4d** involves general base assisted nucleophilic attack of water[18] upon the cation **3d** and that the reverse reaction is general-acid catalyzed (eq 13). Such a situation requires the

$$3 + H_2O + B \underset{k_{BH}}{\overset{k_B}{\rightleftharpoons}} 4 + BH^+ \qquad (13)$$

addition of a term $k_B[B]$ to $k_f$ (eq 11a) and of a term $k_{BH}[BH^+]$ to $k_d$ (eq 11b). Since both [B] and [BH$^+$] are proportional to $[B]_t$, the total buffer concentration at a given pH, this requires that $k_{obsd}$ should be directly proportional to $[B]_t$.

Table IV shows values of $k_{obsd}$ obtained at various concentrations of Tris at four pHs in the region where the deviations are apparent in Figure 3. In each case $k_{obsd}$ increases linearly[19] with $[B]_t$, thereby supporting the involvement of buffer catalysis, presumably due to the operation of the mechanism above (eq 13). As remarked earlier, the deviations from the curve for **1c** in Figure 2 may also be due to buffer catalysis, and so these may also be manifestations of the operation of eq 13.

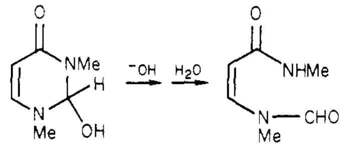
**Table IV. Buffer Catalysis of 3d ⇄ 4d**[a]

| pH | $10^2$[Tris], M | $10^2$[HBr], M | $k_{obsd}$, $s^{-1}$ | least squares[b] |
|---|---|---|---|---|
| 7.77 | 0.594 | 0.375 | 14.2 | $m$ = 197.7 |
| | 0.891 | 0.562 | 14.7 | $c$ = 13.03 |
| | 1.19 | 0.750 | 15.5 | $r$ = 0.9993 |
| | 2.38 | 1.50 | 17.7 | |
| | 3.17 | 2.00 | 19.3 | |
| 8.07 | 1.55 | 0.870 | 30.1 | $m$ = 307.9 |
| | 2.75 | 1.55 | 33.3 | $c$ = 25.00 |
| | 3.67 | 2.06 | 35.7 | $r$ = 0.9939 |
| 8.45 | 2.06 | 0.773 | 73.7 | $m$ = 636.3 |
| | 2.75 | 1.03 | 79.2 | $c$ = 61.39 |
| | 5.50 | 2.06 | 97.9 | $r$ = 0.9972 |
| | 7.33 | 2.75 | 107 | |
| 8.69 | 2.25 | 0.619 | 134 | $m$ = 1121 |
| | 3.00 | 0.825 | 144 | $c$ = 109.6 |
| | 6.00 | 1.65 | 177 | $r$ = 0.9997 |
| | 8.00 | 2.20 | 199 | |

[a] At 30 °C, [KBr] = 0.1 M. [b] Analysis of $k_{obsd}$ vs. [Tris]: $m$ = slope, $c$ = intercept, and $r$ = correlation coefficient.

As pointed out before,[11] it is probable that the rate constant $k_1$ represents water acting as the general base in eq 13 and that $k_{-1}$ represents hydronium ion acting as the general acid. On the other hand, $k_{OH}$ likely corresponds to direct attack by hydroxide ion since there would be no thermodynamic advantage if it acted as a general base[18,20] (cf. ref 5b and 11).

It should be noted that while the pseudobase **4d** is stable enough to be observed[7] and to permit the stopped-flow kinetic experiments discussed above, it does undergo irreversible ring opening in alkaline media.[7,21] We find that **4d** disappears with $k_1^{obsd} = 1.98 \times 10^{-3}$ $s^{-1}$ ($t_{1/2}$ = 350 s) at pH 8.70. Assuming this is due to catalysis by hydroxide ion only, the second-order rate constant for this is 267 $M^{-1}$ $s^{-1}$. The disappearance of the 289-nm band of **4d**[7] is accompanied by the appearance of a new band ~260 nm which may be due to the $\beta$-formamidoacrylamide derivative **10**. Various derivatives of the form RCONHCH=CHCONHR′ have $\lambda_{max}$ in the region 257–263 nm.[22] At longer times the 260-nm band disappears presumably due to hydrolysis of the formamide moiety.[7]



**4d** **10**

**Quantitative Aspects.** Assuming now the validity of the mechanism in eq 1 and the various equations used to describe the experimental data, we can extract or estimate various constants for the four substrates studied (see Table V). Moreover, we can estimate that extent of hydration of **1a,c** and **2b**.

The constants $k_2K_{R^+}$ and $k_1$ in Table V are those which were used to calculate the curves for Figures 1 and 2 by

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[17] Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1973**, *51*, 1965–1972.

[18] The attack of water and alcohols upon the *N,O*-trimethylenephthalimidium cation is general-base catalyzed. Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 489–499, 499–507, 507–515.

[19] Since the data in Table IV give four reasonably straight lines, they are not displayed separately (see least-squares parameters).

[20] Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731–4732.

[21] For related examples see: David, S.; Hirshfeld, H. *Bull. Soc. Chim. Fr.* **1966**, 527–529 and also ref 6 above.

[22] Moore, R. E.; Woolard, F. X.; Younus Sheikh, M.; Scheuer, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 7758–7759.

Table V. Summary of Constants for **1a**, **2b**, **1c**, and **3d**[a]

| constants | units | substrate 1a | 2b | 1c | 3d |
|---|---|---|---|---|---|
| $k_1k_2/k_{-1} = k_2K_{R^+}$ | $s^{-1}$ | 40.0 | 121 | 21.3 | 97.5 |
| $k_1$ | $s^{-1}$ | 0.23 | 0.29 | 0.10 | 0.26[b] |
| $k_2$ | $M^{-1}\ s^{-1}$ | $\sim 10^9$ | $\sim 3 \times 10^9$ | $\sim 10^9$ | $3.3 \times 10^9$ |
| $k_{-1}$ | $M^{-1}\ s^{-1}$ | $\sim 6 \times 10^6$ | $\sim 7 \times 10^6$ | $\sim 5 \times 10^6$ | $8.8 \times 10^6$[b] |
| $K_{R^+} = k_1/k_{-1}$ | M | $\sim 4 \times 10^{-8}$ | $\sim 4 \times 10^{-8}$ | $\sim 2 \times 10^{-8}$ | $2.95 \times 10^{-8}$ |
| $pK_{R^+}$ | | $\sim 7.4$ | $\sim 7.4$ | $\sim 7.7$ | 7.53[c] |
| $pK_1$ (fitted) | | 1.80 | 2.00 | 1.87 | |
| $pK_1$ (lit.) | | 1.85,[d] 1.69[e] | 2.02[f] | 1.84[e] | |
| $K_{R^+}/K_1$[g] | | $\sim 2.5 \times 10^{-6}$ | $\sim 4 \times 10^{-6}$ | $\sim 1.5 \times 10^{-6}$ | |

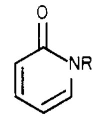
[a] At 30 °C, $\mu = 0.11$ M. Constants preceded by an approximate sign are estimated; the others are derived from experimental data (see text). [b] From a bromination study. Equilibration study gave $k_1 = 0.2\ s^{-1}$ and $k_{-1} = 7 \times 10^6\ M^{-1}\ s^{-1}$. [c] From ref 7. [d] Albert, A.; Brown, D. J.; Cheeseman, G. J. *Chem. Soc.* **1951**, 474–486. [e] Reference 9. [f] Reference 8a. [g] Equals [covalent hydrate]/[4-pyrimidinone].

using the appropriate equations given above. Since $K_{R^+}$ is known for **3d**,[7] we have $k_2 = 3.3 \times 10^9\ M^{-1}\ s^{-1}$ for attack of bromine upon the pseudobase **4d**.[23] Also from $k_1$ and $K_{R^+}$ we have $k_{-1} = 8.8 \times 10^6\ M^{-1}\ s^{-1}$ ($7 \times 10^6$ from equilibration). Thus all the entries for **3d** in Table V are based firmly on experiment.

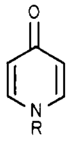
For the other substrates $K_{R^+}$ is not directly measurable but may be estimated as follows. Attack of bromine upon the covalent hydrate **4b** probably has a $k_2$ value close to that for **4d** (say $\sim 3 \times 10^9\ M^{-1}\ s^{-1}$), since both have $R_1$ = Me. For the covalent hydrates **4a** and **4c**, both of which have $R_1$ = H, one expects a slightly smaller $k_2$ of $\sim 10^9\ M^{-1}\ s^{-1}$. Using these estimates of $k_2$ and the values of $k_2K_{R^+}$ used in fitting, we can estimate $K_{R^+}$ for the covalent hydrates **4a–c**. From these in turn can be obtained values of $k_{-1}$ by using $k_1$ derived from the data.

For all four substrates the constants in Table V are very similar, in accord with them all reacting via the mechanism in eq 1. Moreover, they are close to those for the isomeric 2-pyrimidinones recently reported by us.[5a] The values of $k_1$ and $k_{-1}$ (and $k$ and $k_{OH}$ for **3d**) are in the general area found for a variety of cation–pseudobase systems.[11] The high values of $k_2 \approx 10^9\ M^{-1}\ s^{-1}$, close to diffusion controlled values, are reasonable for attack of bromine upon an enamine, albeit somewhat a deactivated[5a,b] one (see **4**, Scheme I).

**Comparison with Pyridinones.** The free base forms of 2(1*H*)-pyridinone (**11a**), 4(1*H*)-pyridinone (**12a**), and their *N*-methyl derivatives (**11b** and **12b**) are attacked by bromine with second-order rate constants $k_2 \approx 10^4\ M^{-1}\ s^{-1}$.[16] The curves in Figure 1 correspond to *apparent* values of $k_2 = 2.9 \times 10^3$, $1.2 \times 10^4$, and $1.6 \times 10^3\ M^{-1}\ s^{-1}$ for bromine attack upon the free base forms of the 4-pyrimidinones **1a**, **2b**, and **1c**, respectively. These values are unreasonable in that the additional aza nitrogen in these pyrimidinones should reduce their reactivity considerably[25] relative to the pyridinones. In fact, from the present data we can set an upper limit for the actual $k_2$ value for direct attack which is substantially lower and much more reasonable.



**11a**, R = H
**b**, R = Me



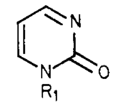
**12a**, R = H
**b**, R = Me

At pH 4.97 bromination of 3-methyl derivative **1c** involves rate-limiting formation of its covalent hydrate with the rate = $k_0^{obsd} = 4.5 \times 10^{-7}\ M\ s^{-1}$ (Table II, Figure 2). Therefore the second-order rate for direct attack of bromine upon **1c** must be much less than this rate (eq 15).

$$k_2[\mathbf{1c}][Br_2]_0 \ll \text{rate} \simeq 5 \times 10^{-7}\ M\ s^{-1} \qquad (15)$$

Insertion of the appropriate concentrations into eq 15 leads to the conclusion $k_2 \ll 5\ M^{-1}\ s^{-1}$ for direct attack upon **1c**. Likewise, for **1a** and **2b** we must have $k_2 \ll 55\ M^{-1}\ s^{-1}$ and $k_2 \ll 40\ M^{-1}\ s^{-1}$, respectively. However, it is probable that a value of $k_2 \ll 5\ M^{-1}\ s^{-1}$ is appropriate for all three substrates.

If the second-order data observed for the bromination of 2-pyrimidinones[5a] **13a** and **13b** is attributed to direct attack by bromine, the *apparent* values of $k_2$ are $5.2 \times 10^5$ and $2.1 \times 10^5\ M^{-1}\ s^{-1}$. These are *greater* than those observed for the 2-pyridinones[16] (**11a,b**) and so are quite unreasonable. In the same manner as used above we have estimated an upper limit of $k_2 \ll 50\ M^{-1}\ s^{-1}$ for direct bromine attack upon **13**.[5a] Again this is much more in keeping with the known deactivating influence of an aza nitrogen.[25]



**13a**, $R_1$ = H
**b**, $R_1$ = Me

**Covalent Hydration.** The degree of covalent hydration of the substrates **1a,c** and **2b** may be estimated from the $pK_1$ values and values of $K_{R^+}$[5a,11] estimated as described above and presented in Table V. For example, for **1a** we have $K_1 = [\mathbf{1a}][H^+]/[\mathbf{3a}] = 10^{-1.80}$ and $K_{R^+} = [\mathbf{4a}][H^+]/[\mathbf{3a}] \simeq 10^{-7.4}$. Therefore, $[\mathbf{4a}]/[\mathbf{1a}] = K_{R^+}/K_1 \simeq 2.5 \times 10^{-6}$ is the extent to which 4(3*H*)-pyrimidinone (**1a**) exists as its covalent hydrate in aqueous solution. The values for the *N*-methyl derivatives **1c** and **2b** are quite similar (Table V). By way of comparison the 2-pyrimidinones **13a,b** have values of $\sim 5 \times 10^{-4}$ and $\sim 1 \times 10^{-4}$, respectively.[5a]

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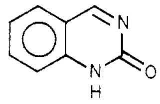
(23) We are assuming here and in the subsequent discussion that molecular bromine is the attacking electrophile. As discussed elsewhere,[24] HOBr and $H_2OBr^+$ are unlikely electrophiles under our conditions ($[Br^-] \geq 0.1$ M and pH 0–5), and tribromide ion is a much weaker electrophile. In an earlier study on 4(3*H*)-quinazolinone (**15**) it was shown that attack by tribromide ion is unimportant.[6] *If* it transpired that some bromination was taking place by way of tribromide ion, then our values of $k_2$ (here and elsewhere[5a,24]) would have to be reduced by an appropriate factor. However, and more importantly, our conclusions concerning the mode of reaction of the heterocycle, and the extent of its covalent hydration, would in no way be affected.

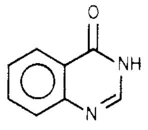
(24) Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830–835.

(25) (a) Katritzky, A. R.; Johnson, C. D. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 608–615. (b) Tomasik, P.; Johnson, C. D. *Adv. Heterocycl. Chem.* **1976**, *20*, 1–64. The value of $\sigma_m^+$ for aza nitrogen is 0.54.

The effect of benzannelation upon covalent hydration can be seen by comparing the pyrimidinones discussed above with the appropriate quinazolinones. In aqueous solution 2(1*H*)-quinazolinone (**14**) exists to the extent of 25% as its covalent hydrate[26] (i.e.; $K_{R^+}/K_1 = 0.33$). Thus, relative to 2(1*H*)-pyrimidinone (**13a**) there is ~1000-fold more hydration ($\Delta\Delta G \approx 4$ kcal/mol) in the case of **14**. This is probably a reflection of the lesser "aromaticity" of the heterocyclic ring of **14** relative to that of **13a**.



14



15

The degree of covalent hydration of 4(3*H*)-quinazolinone (**15**) is not known,[27] although its covalent hydrate is involved in its bromination in aqueous solution.[6] Thus comparison between **15** and **1a** is not possible at this time.

## Conclusions

In aqueous solution the 4-pyrimidinones **1a**, **2b**, and **1c** exist to a very limited extent (~0.0001%) as their covalent hydrates (**4a–c**). Nevertheless, at pH <5 bromination ensues by way of attack upon these covalent hydrates because they are so reactive toward bromine ($k_2 \approx 10^9$ M$^{-1}$ s$^{-1}$). Indeed, at pH >2.5 formation of **4** from **3** is the rate-determining step, whereas at pH <2.5 attack of bromine upon **4** is rate-limiting. The primary steps **3** $\rightleftarrows$ **4** $\rightarrow$ **5** of the mechanism shown in Scheme I are thus substantiated. Since the remaining steps are based on an earlier study,[7] the entire mechanism in Scheme I is supported.

Our results demonstrate quite dramatically the effect that covalent hydrates may have upon reactivity. For direct attack by bromine upon 4(3*H*)-pyrimidinone (**1a**) a value of $k_2 \ll 5$ M$^{-1}$ s$^{-1}$ is indicated. However, by virtue of it reacting via its covalent hydrate, it has an *apparent* value of $k_2 = 2.9 \times 10^3$ M$^{-1}$ s$^{-1}$, and thus its reactivity is enhanced by ≫580 times. For 2(1*H*)-pyrimidinone (**13a**) the enhancement is even greater at ≫$10^4$ times due to its greater extent of covalent hydration.

## Experimental Section

The origins of the substrates (**1a**, **2b**, **1c**, and the **3d** perchlorate salt) were the same as noted previously,[7] although some **1a** was obtained from commercial sources and recrystallized before use. In many instances the hydrobromide salts of **2b** and **1c** were used since they recrystallize more easily and show greater long-term stability. These salts gave appropriate UV, IR, and $^1$H NMR spectra.

For the most part the solutions used in kinetics experiments were 0.1 M in potassium bromide and had $\mu = 0.11$ M.[5a,b] At high acidities solutions had [KBr] + [HBr] ≃ 1.1 M (see text). Kinetics experiments were carried out at 30 °C by using a stopped-flow apparatus and a transient recorder employed in earlier work.[5a,b,24] Bromine disappearance was measured by using the decrease in absorbance by $Br_3^-$ in the 267–290-nm region relative to little or no change occurring at 320 nm.[5b]

Each of the rate constants quoted in the text is the average of 3–5 runs differing by <10%, although in most cases they differed by <5%.[5b] First-order rate constants were obtained from least-squares analysis[28] of $\ln (A - A_\infty)$ vs. time for absorbance data covering ~90% reaction (3–4 half-lives). In several cases values of $A_\infty$ were not stable due to the elimination **7** $\longrightarrow$ **9**[7] (Scheme I). For these cases $A_\infty$ was obtained by the Kezday–Swinbourne method.[29] Rate constants were also obtained by the Guggenheim method[29] for comparitive purposes.

Zero-order rate constants were obtained as described previously.[5b] Most of the second-order rate constants given in the text are derived from pseudo-first-order rate constants, taking into account the substrate concentration[5e] and the depletion of bromine due to tribromide ion formation.[24] Some experiments were carried out where the excess of substrate over bromine was not large, and so the absorbance data was analyzed directly for second-order behavior (see entries in Table I with a superscript *e*). The total absorbance change ($A_0 - A_\infty$) was equated with the consumption of all the initial bromine concentration. By use of the apparent extinction coefficient thus obtained, concentrations of substrate and bromine at various times were calculated from the absorbance data covering ~90% reaction. These were analyzed by least-squares methods on the basis of the second-order equation $\ln (b - x)/(a - x) = \ln b/a - (a - b)k_2t$, where $a$ (the initial substrate concentration) > $b$ (the initial bromine concentration), and $x$ is the amount consumed after time $t$. The apparent second-order rate constants which were obtained from such analysis[28] were corrected for tribromide ion formation[24] to give values whose averages are quoted in the text.

Analysis of the mixed zero-order and first-order data was based upon the integrated form of eq 2, as detailed elsewhere.[5a]

Studies of the equilibration of the cation **3d** and its pseudobase **4d** followed established procedures.[5b,11,17] The appearance or disappearance of **4d** was monitored at 289 nm relative to little or no change at 320 nm.

**Acknowledgment.** We thank the Natural Sciences and Engineering Research Council of Canada for providing operating grants to O.S.T. and a post-graduate scholarship to M.P.

**Registry No.** **1a**, 4562-27-0; **1c**, 6104-45-6; **2b**, 2228-30-0; **3d**, 78513-97-0; **4d**, 78513-98-1; **10**, 78513-99-2.

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(26) Albert, A.; Howell, C. F. *J. Chem. Soc.* **1962**, 1591-1596.

(27) Estimation of the degree of covalent hydration of **15** from bromination data[6] is not possible due to the lack of a reasonably accurate value of $K_{R^+}$ for its dimethyl derivative.[6]

(28) Only those runs which gave $r \geq 0.9995$ (for 12-20 points) in least-squares analysis were considered acceptable.

(29) Swinbourne, E. S. "Analysis of Kinetic Data"; Nelson: London, 1971; pp 78-84.