Kinetics of the Reaction of Bromine with 5-Bromo-2(1*H*)-pyrimidinones: Evidence for the Involvement of Covalent Hydrates

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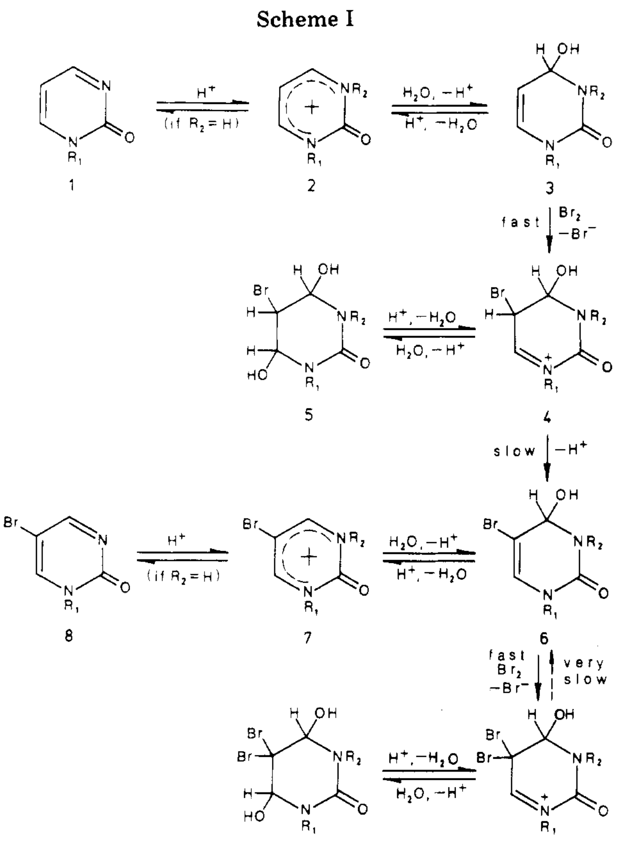
The kinetics of bromination of 5-bromo-2(1*H*)-pyrimidinone, 5-bromo-1-methyl-2-pyrimidinone, and 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium bromide have been measured in 2–13 N aqueous sulfuric acid. In these media all three substrates exist (>99%) as cations. The order of reaction, the acidity dependence of the rates, and the reactivities of the substrates are all consistent with a mechanism in which the rate-determining step involves attack by molecular bromine upon the covalent hydrate (or pseudobase) of the substrates.

We have previously presented evidence that the bromination of simple 2(1*H*)-pyrimidinones carried out in aqueous acidic media proceeds in several discrete steps,[1] as shown in Scheme I. In the first step, the covalent hydrates (or pseudobase) 3, in equilibrium with substrates 1 (or 2), react *rapidly* with bromine to give 4 and hence the observable[1] intermediates 5. These nonaromatic intermediates undergo *slow* acid-catalyzed[1] dehydration via 4 to give the isolable 5-bromo derivatives 8 (or 7). In the presence of a sufficiency of bromine a further reaction takes place, presumably via the covalent hydrates (or pseudobase) 6, to give 5,5-dibromo derivatives[1] 10.

Scheme I



We hoped that by using more concentrated acidic media we would be able to study the first steps of the reaction ($2 \rightleftarrows 3 \rightarrow 4 \rightleftarrows 5$), and thus obtain more direct evidence of the intermediacy of the covalent hydrate 3. For the cation 2 ($R_1 = R_2$ = Me) the equilibrium constant[2] $K_{ROH} = [3][H^+]/[2] = 10^{-7}$. Thus, in strong acid the concentration of 3 should be very low, and hence the rate of bromine consumption might be reduced to a measurable quantity. However, the conversion $5 \rightarrow 6 \rightleftarrows 7$ is acid catalyzed,[1] and in strong acid it seems that its rate is sufficiently fast that 6 can compete with 3 for bromine. Consequently, in strong acid the rate of disappearance of bromine follows complex kinetics which we have not pursued. We were, however, able to study the bromination $7 \rightarrow 10$ (R_1, R_2 = H, or Me) for which the covalent hydrates (or pseudobase) 6 were previously proposed[1] as the actual intermediates undergoing electrophilic attack.

Results and Discussion

We have studied the kinetics of the reaction between bromine and the substrates 5-bromo-2(1*H*)-pyrimidinone (**8**, R_1 = H), 5-bromo-1-methyl-2-pyrimidinone (**8**, R = Me), and 5-bromo-1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium (**7**, $R_1 = R_2$ = Me) bromide in 2–13 N aqueous sulfuric acid, in which all three substrates largely (>99%) exist as cations.[3] In media of acidity greater than 15 N sulfuric acid, a quantitative reaction between bromine and the substrates was not observed. At these acidities, bromine could be detected even in the presence of a tenfold excess of substrate. This we presume to be due to the onset of the acid-catalyzed reverse reaction[4] $10 \rightarrow 9 \rightarrow 6 \rightarrow 7$ which we observed earlier.[1] However, at acidities less than 15 N sulfuric acid the reaction with bromine proceeds to completion, and the decrease in UV absorbance due to bromine (or substrate) follows first-order kinetics if the substrate is present in excess (about tenfold).

Substrate Dependence. In the presence of an excess of substrates, good pseudo-first-order rate constants (k_1^{obsd}) were obtained for the bromination of all three substrates. By varying the substrate concentration it was shown that the reactions are in fact second order (see Table I).

The conditions of our experiments were not truly pseudo-first-order in that the excess of substrate over bromine was not very large (5- to 13-fold). However, one can still obtain useful results under these circumstances. For a second-order reaction $\ln [(b - x)/(a - x)] = \ln (b/a) - (a - b)k_2t$. If $b < a \gg x$, this may be simplified to $\ln (b - x) = \ln b - (a - b)k_2t$. Thus, during the earlier stages of the reaction, when $a \gg x$ is most valid, the disappearance of the component b follows a first-order law for which the apparent pseudo-first-order rate constant $k_1^{obsd} = (a - b)k_2$. In the present work, therefore, second-order rate constants were calculated from $k_2^{obsd} = k_1^{obsd}/([7] - [Br_2]_0)$. This approach has been used previously by Bell,[5a] and by us.[5b,c]

Acidity Dependence. Table II shows the second-order rate constants that were obtained for reactions carried out in various concentrations of sulfuric acid. For all three substrates the rate of bromination decreases markedly with increasing acidity, and presumably this reflects the diminishing concentration of the covalent hydrates (or pseudobase) 6.

Since the equilibrium $7 \rightleftarrows 6$ is a type of carbenium ion-carbinol interconversion, we have chosen to use the acidity function H_R (derived from the ionization of carbinols)[6] as the measure of acidity. Plots of $\log k_2^{obsd}$ vs. H_R give good straight

Table I. Substrate Dependence of the Rates of Bromination of 7 at 30 °C

7						
R_1	R_2	$[7] \times 10^4$, M	$[Br_2]_0 \times 10^5$, M	$k_1^{obsd} \times 10^2$, s^{-1}	k_2^{obsd}[a], $M^{-1} s^{-1}$	Av k_2^{obsd}, $M^{-1} s^{-1}$
H	H[b]	2.0	4.9	5.19	344	
			4.1	5.00	314	332 ± 18[c]
		4.0	5.6	11.7	340	
			5.4	11.4	329	
Me	H[d]	2.0	4.0	7.91	494	
			2.0	8.72	484	
		3.0	3.0	13.2	489	
			3.0	13.0	481	488 ± 12[c]
			3.0	13.4	496	
		4.0	3.0	17.6	476	
			3.0	18.4	497	
Me	Me[d]	2.0	2.7	2.91	168	
			2.7	2.86	165	
		3.0	4.5	4.08	160	
			4.5	4.14	162	162 ± 6[c]
		4.0	5.5	5.50	159	
			5.5	5.55	161	
			5.5	5.39	156	

[a] $k_2^{obsd} = k_1^{obsd}/([7] - [Br_2]_0)$. [b] In 7.4 N H_2SO_4. [c] Maximum deviation from average. [d] In 5.55 N H_2SO_4.

Table II. Acidity Dependence of the Rates of Bromination[a] of 7 at 30 °C

7						
R_1	R_2	$[H_2SO_4]$, N	$-H_R$	k_2^{obsd}, $M^{-1} s^{-1}$	$\log k_2^{obsd}$	No. of runs
H	H	5.90	1.99	1210	3.083	2
		7.01	2.58	492	2.692	4
		7.40	2.75	332	2.521	4
		8.64	3.44	103	2.013	5
		10.0	4.14	24.6	1.391	3
Me	H	5.55	1.79	488	2.688	7
		6.50	2.30	197	2.294	4
		8.05	3.10	46.4	1.667	3
		9.95	4.14	7.25	0.860	2
Me	Me	2.00	0.11	3830	3.583	4
		2.76	0.45	1890	3.276	3
		4.00	1.02	622	2.794	8
		5.55	1.79	162	2.210	7
		9.50	3.90	4.10	0.6128	6
		11.4	4.93	0.610	−0.2147	2
		13.3	5.94	0.120	−0.9208	2

[a] Each k_2^{obsd} is the average of the number of runs indicated in the last column.

Table III. Least-Squares Analysis of log k_2^{obsd} vs. H_R for 7 → 10

7		Intercept	Slope		No.
R_1	R_2	= log k_2K (SD)	= m (SD)	Corr coeff	of pts
H	H	4.69 (0.02)	0.79 (0.03)	0.9984	5
Me	H	4.08 (0.001)	0.78 (0.001)	0.9999	4
Me	Me	3.62 (0.01)	0.77 (0.007)	0.9998	7

lines with slopes about 0.78 (see Table III). These observations, we believe, are completely compatible with the intermediacy of the species **6**.

Electrophilic attack upon the cations **7** is unlikely,[7] and would not result in the observed inverse dependence of rate upon acidity. The cation **7** ($R_1 = R_2 =$ Me) almost certainly reacts via the observable[1b] pseudobase **6** ($R_1 = R_2 =$ Me), this being an enamine and thus highly susceptible to electrophilic attack. In view of the similarity in their rates of bromination, and in the acidity dependences, it is reasonable to propose that the other two substrates **7** ($R_1 = R_2 =$ H) and **7** ($R_1 =$ Me, $R_2 =$ H) react via their covalent hydrates **6** ($R_1 = R_2 =$ H) and **6** ($R_1 =$ Me, $R_2 =$ H),[10] respectively.

For the proposed mechanism

$$H_2O + \mathbf{7} \overset{K}{\rightleftharpoons} H^+ + \mathbf{6} \xrightarrow[Br_2]{k_2} \mathbf{9} \rightarrow \mathbf{10}$$

we should have

$$k_2^{obsd} = k_2K/h_x \tag{1}$$

and

$$\log k_2^{obsd} = \log k_2K + H_x \tag{2}$$

where $K = [6]h_x/[7]$, and $H_x = -\log h_x$ is the acidity function, defined like H_R,[6] governing the equilibrium. Equations 1 and 2 are derived assuming $[7] \gg [6]$ (or $h_x \gg K$) which is justifiable, since for **7** ($R_1 = R_2 =$ Me) we have previously measured[1b] $K = 10^{-3.08}$.

The observed data in Table II can be expressed in the form $\log k_2^{obsd} =$ intercept $+ mH_R$ (see Table III) which is in accord with eq 2 in view of the known linear relationship between acidity functions.[11] Accordingly, the data also support the proposed mechanism.

Relative Reactivities. Finally, we consider the reactivities of the substrates **7** in terms of the mechanism proposed above. Assuming that $H_x = mH_R$, we can equate the intercepts in Table III with the term log k_2K from eq 2. Except for the dimethyl cation **7** ($R_1 = R_2 = Me$) the term k_2K is not separable, and so we compare these terms for the three substrate cations.

cation 7	$R_1 = R_2 = H$	$R_1 = Me$ $R_2 = H$	$R_1 = R_2 = Me$
k_2K, s^{-1} (30 °C)	4.9×10^4	1.2×10^4	4.2×10^3
rel	11.7	2.86	1.00

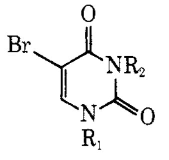
Methyl substitution should increase k_2, but decrease K for steric and electronic reasons.[2] It appears that the second effect is dominant.[12] This is not unreasonable, since it is known that steric factors play a significant role in the equilibria **2** ⇄ **3**,[2] and the presence of the 5-bromo substituent in **7** should enhance the hindrance to hydroxyl attachment resulting from methyl substitution.[2]

A similar order of reactivity was observed earlier in the H–D exchange of the cations **2** in aqueous acid.[13] For this reaction we proposed that the rate-determining step involved electrophilic attack by D$^+$ upon **3**.[13]

cation 2	$R_1 = R_2 = D$	$R_1 = R_2 = Me$
k_2K, s^{-1} (107 °C)	4.7×10^{-5}	7.2×10^{-6}
rel	6.5	1.0

For the dimethyl cation **7** ($R_1 = R_2 = Me$) the equilibrium constant[1b] $K \simeq 10^{-3}$, and so $k_2 \simeq 4 \times 10^6$ M^{-1}s^{-1}. This value for the attack of bromine upon the pseudobase **6** ($R_1 = R_2 = Me$) seems to us quite reasonable. The enol of acetone reacts with bromine with $k_2 \simeq 10^7$ M^{-1}s^{-1} at 25 °C.[14] A simple enamine should be more reactive than this,[15] but in **6** the enamine moiety would be deactivated by the presence of the 5-bromo substituent and by the carbonyl group in conjugation with the N$_1$ lone pair.

It is, perhaps, noteworthy that similarly substituted 5-bromouracils (**11**), which have a carbonyl group at position 4, are much less reactive.[16]



11

$R_1 = R_2 = H$, $k_2 = 64$ M^{-1}s^{-1}

$R_1 = R_2 = Me$, $k_2 \simeq 19$ M^{-1}s^{-1}

In summary, we feel that the relative and the absolute reactivities of the substrates **7** are understandable in terms of the proposed mechanism involving **6**. It may be noted that of the species **1**–**10** in Scheme I only **4** and **9** have not been directly observed.[1]

Experimental Section

The origin of the compounds used in this study, their UV spectral data, and their pK values can be found elsewhere.[1b] UV measurements were made on a Cary 14 instrument and on an Aminco DW-2.

Sulfuric acid solutions were either commercial standard volumetric solutions, or were made by dilution of concentrated sulfuric acid (38 N) and were checked by titration against a standard sodium hydroxide solution.

Values of H_R were obtained by interpolation from the data (at 30 °C) of Arnett and Bushick[6] using "Wt % H_2SO_4" calculated from "normality" and the known densities of sulfuric acid–water mixtures.[17]

Constant temperature was maintained by circulation of water at 30.00 ± 0.05 °C through the cell holders of the spectrophotometer. Reagent solutions were equilibrated at 30 °C prior to their use in kinetic experiments.

The rate of the reaction between the substrates **7** and bromine was measured by monitoring the decrease in absorbance due to bromine or the substrate[18] at a convenient UV wavelength. A solution of the final product mixture with an absorbance approximately equal to A_∞ was used as a reference to largely offset the absorbance due to the unreacted excess of substrate.

Reactions were initiated by adding 50 or 100 μL of bromine solution to a 1-cm cell and then adding 3 mL of substrate solution. Between 10 and 15 absorbance values were taken over 2 half-lives, and pseudo-first-order rate constants (k_1^{obsd}) were obtained from least-squares analysis of ln ($A - A_\infty$) vs. time. Only those data which gave correlation coefficients ≥0.9995 were accepted. The rate constants reported in the text are the averages of two to eight individual runs.

Second-order rate constants (k_2^{obsd}) were obtained from[5] $k_2^{obsd} = k_1^{obsd}/([7] - [Br_2]_0)$ as explained in the text. Since the loss of bromine from aqueous solutions is appreciable over extended periods of time, the actual bromine concentration for a given kinetic run was estimated from the total change in absorbance due to the decrease in the substrate concentration assuming $[Br_2]_0 = [7]_0 - [7]_\infty$.

Up to 0.01 M KBr had a negligible effect upon the rates. Since [Br$^-$] did not exceed 10^{-3} M during any of the kinetic experiments, its effect upon the rate constants (due to tribromide ion formation) was ignored.

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Registry No.—**7** ($R_1 = R_2 = Me$) bromide, 38353-08-1; **8** (R_1 = H), 38353-06-9; **8** (R_1 = Me), 14248-01-2; bromine, 7726-95-6.

References and Notes

(1) (a) O. S. Tee and S. Banerjee, *J. Chem. Soc., Chem. Commun.*, 1032 (1972); (b) O. S. Tee and S. Banerjee, *Can. J. Chem.*, **52**, 451 (1974).

(2) The K_{ROH} values for 11 different cations **2** have been determined. O. S. Tee and M. Endo, *Can. J. Chem.*, **54**, 2681 (1976).

(3) The relevant pK values are given in ref 1b.

(4) Acid-catalyzed, bromide ion induced debrominations have been observed in related compounds. S. Banerjee and O. S. Tee, *J. Org. Chem.*, **39**, 3120 (1974).

(5) (a) R. P. Bell and E. N. Ramsden, *J. Chem. Soc.*, 161 (1958); (b) O. S. Tee and G. V. Patil, *J. Org. Chem.*, **41**, 838 (1976); (c) S. Banerjee and O. S. Tee, *ibid.*, **41**, 4004 (1976).

(6) E. M. Arnett and R. D. Bushick, *J. Am. Chem. Soc.*, **86**, 1564 (1964).

(7) Unlikely, since it would involve a dicationic transition state. Note, however, that electrophilic attack upon heterocyclic cations is not unknown, e.g., nitration and hydrogen isotope exchange of various pyridines in strong acid,[8] bromination, iodination, and hydrogen isotope exchange of 2,3-dihydro-1,4-diazepinium cations.[9]

(8) A. R. Katritzky and C. D. Johnson, *Angew. Chem., Int. Ed. Engl.*, **6**, 608 (1967).

(9) R. P. Bell and D. R. Marshall, *J. Chem. Soc.*, 2195 (1964); C. Barnett and J. Warkentin, *J. Chem. Soc., B*, 1572 (1968).

(10) We prefer the covalent hydrate **6** (R_1 = Me, R_2 = H) rather than **6** (R_1 = H, R_2 = Me) for steric reasons. For the cations **2** the hydroxyl group is attached preferentially to the position adjacent to the least bulky substituent.[2] The presence of the 5-bromine probably enhances this preference.[2]

(11) K. Yates and R. A. McClelland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).

(12) In the bromination of 4(3*H*)-quinazolinones, which also involves covalent hydrates, the opposite is true; that is, the effect on k_2 is dominant.[5b]

(13) A. R. Katritzky, M. Kingsland, and O. S. Tee, *J. Chem. Soc., Chem. Commun.*, 289 (1968); *J. Chem. Soc., B*, 1484 (1968).

(14) K. Yates and W. V. Wright, *Can. J. Chem.*, **41**, 2882 (1963); R. P. Bell and G. G. Davies, *J. Chem. Soc.*, 902 (1964).

(15) The iodination of acetone shows apparent acid catalysis by primary and secondary (but not tertiary) ammonium ions. This has been attributed to rate-determining formation of an enamine which reacts rapidly with iodine. M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2504 (1966).

(16) O. S. Tee and C. G. Berks, unpublished results.

(17) "International Critical Tables", Vol. **3**, 1928, p 56.

(18) Even though the change in substrate absorbance is relatively small it can be measured successfully on the more sensitive Aminco DW-2. Rates measured by following bromine decrease and substrate decrease agree very well.