should not be significantly different from that of the transition state of anti eliminations.

Experimental Section

Materials. *trans*-2,3-Dichloro-2,3-dihydrobenzofuran (1),[10] *trans*-2,3-dichloro-2,3-dihydro-3-deuteriobenzofuran (2),[15] and *trans*-2,3,5-trichloro-2,3-dihydrobenzofuran (3) were prepared by chlorine addition in Et_2O at −5 to 0 °C to the corresponding benzofuran.[10] The NMR spectrum (CCl_4) of 3 exhibited the following peaks: δ 5.32 (1 H, s, 3-H), 6.40 (1 H, s, 2-H), 6.82–7.50 (3 H, m, ArH). The UV spectra (99% Me_2SO) of these compounds exhibited very broad maxima at 284 (1 and 2) and 296 nm (3). 3-Chlorobenzofuran[10] and 3,5-dichlorobenzofuran were obtained by dehydrohalogenation of 1 and 3, respectively, with alcoholic potassium hydroxide.[10] The NMR spectrum (CCl_4) of the latter compound exhibited the following peaks: δ 7.51 (1 H, s, 2-H), 7.05–7.55 (3 H, m, ArH). The UV spectra (99% Me_2SO) exhibited very sharp absorption maxima at 277 and 284 nm (3-chlorobenzofuran) and at 284 and 292 nm (3,5-dichlorobenzofuran). 4-Chloro-2-nitroaniline (Fluka AG) and phenol and its derivatives (Erba RPE) were used without further purification.

The solvent and bases were prepared as previously described.[15]

Kinetic Study. Kinetic experiments were carried out by following spectrophotometrically the disappearance of the base at 330 nm for phenoxide and *p*-methyl-, *p*-chloro-, and *p*-bromophenoxide, 480 nm for *m*-nitrophenoxide, and 560 nm for 4-chloro-2-nitroanilide. At these wavelengths no appreciable absorbance is exhibited by the reaction products. The reactions were brought about in a stoppered two-limbed silica cell. In one limb was placed the substrate solution (1 mL), and in the other was placed at first the phenol solution (1 mL) and then successively, under nitrogen, an amount of 0.0116 M tetraethylammonium hydroxide solution calculated on the basis of previous spectrophotometric titration of the phenol solution as described in the literature[28] (100–200 μL). The cell was placed in the thermostated compartment of a Beckman DB-GT spectrophotometer. After 20 min the solutions were mixed throughly, and the cell was rapidly placed again in the cell compartment of the spectrophotometer. The final product from the reactions of 1–3 with *m*-nitrophenoxide was the corresponding 3-chlorobenzofuran as shown by comparison (GPC analysis[10] at 120 °C) with an authentic specimen.

Acknowledgment. This work was carried out with the financial support of the Italian National Council of Research (CNR). We are also grateful to Professor F. G. Bordwell for making available results to us prior to publication.

Registry No. 1, 63361-57-9; 2, 70749-80-3; 3, 72360-51-1; *p*-$CH_3C_6H_4O^-$, 3174-48-9; $C_6H_5O^-$, 3229-70-7; *p*-$ClC_6H_4O^-$, 24573-38-4; *p*-$BrC_6H_4O^-$, 2042-41-3; *m*-$NO_2C_6H_4O^-$, 14609-74-6; 4-Cl-2-$NO_2C_6H_3NH^-$, 72360-52-2.

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Mechanisms of Bromination of Uracil Derivatives. 5.[1] Reaction of Uracil and 5-Bromouracil via Their Anions in Weakly Acidic Aqueous Solution

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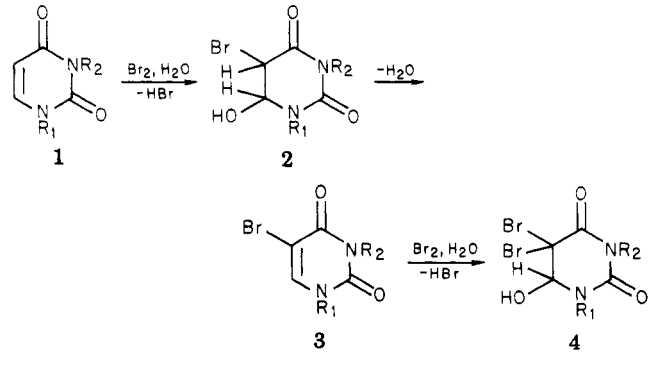
The rates of reaction of bromine with uracil, 1-methyluracil, 3-methyluracil, 1,3-dimethyluracil, 5-bromouracil, and 5-bromo-1,3-dimethyluracil have been measured in acidic, aqueous solutions (pH 0–5). For those derivatives having a methyl group at N_1 the observed second-order rate constants are invariant with acidity, whereas for those derivatives having hydrogen at N_1 they increase with decreasing acidity. These results suggest that reaction upon the anions of uracil, 3-methyluracil, and 5-bromouracil predominates at higher pH. The mechanistic implications of these findings are discussed.

In a recent paper[1] we presented evidence which supports the overall mechanism of bromination of uracils in aqueous solution first proposed by Wang.[2] In this mechanism (Scheme I) bromine reacts rapidly with the uracil 1 (R_1 and R_2 = H or Me), leading to an observable[1] intermediate, 2, which undergoes relatively slow dehydration to give the substitution product 3, a 5-bromouracil. Details of the mechanism of the conversion 2 → 3 were afforded by a kinetic study of the appearance of 3 in acidic media.[1] 5-Bromouracils 3 also react with aqueous bromine and yield 5,5-dibromo derivatives 4.[2] The reverse reaction, 4 → 3, which occurs in strong acid,[2] has been studied kinetically for the 6-methyl homologue.[3]

Heretofore no study of the fast reactions of bromine with uracils 1 or 5-bromouracils 3 has appeared. In this paper we report such a study carried out by using the stopped-flow method, the object being to provide mechanistic details of the steps 1 → 2 and 3 → 4.

Scheme I



Results

We have measured the rates of reaction of bromine with uracil (1, R_1 = R_2 = H), 1-methyluracil (1, R_1 = Me, R_2 = H), 3-methyluracil (1, R_1 = H, R_2 = Me), 1,3-di-

(1) Part 4: O. S. Tee and S. Banerjee, *Can. J. Chem.*, **57**, 626 (1979).
(2) S. Y. Wang, *J. Org. Chem.*, **24**, 11 (1959).
(3) S. Banerjee and O. S. Tee, *J. Org. Chem.*, **39**, 3120 (1974).

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Table I. Substrate Dependence of Rates of Disappearance of Bromine Due to Reaction with Uracils 1 or 3[a]

uracil, medium acidity	10^4[uracil], M	k_1^{obsd}, s^{-1}	k_1^{calcd}, s^{-1}
1 ($R_1 = R_2 = H$), 0.5 M H_2SO_4, $H_0 = 0.11$	5.0	8.41	8.57
	10.0	17.0	17.0
	15.0	25.8	25.4
	20.0	33.5	33.8
1 ($R_1 = R_2 = H$), buffer, pH 4.64	5.0	17.5	17.8
	7.5	28.2	27.6
	10.0	37.2	37.5
1 ($R_1 = R_2 = Me$), 0.05 M H_2SO_4, pH 1.26	5.0	16.3	15.7
	7.5	24.0	25.0
	10.0	34.7	34.3
	15.0	53.0	52.9
3 ($R_1 = R_2 = H$), 0.5 M H_2SO_4, $H_0 = 0.11$	5.0	1.04×10^{-2}	1.03×10^{-2}
	7.5	1.55×10^{-2}	1.58×10^{-2}
	10.0	2.14×10^{-2}	2.13×10^{-2}
3 ($R_1 = R_2 = Me$), 0.09 M H_2SO_4, pH 1.03	2.5[b]	1.80×10^{-3}	1.75×10^{-3}
	5.0	3.19×10^{-3}	3.29×10^{-3}
	7.5	5.06×10^{-3}	5.01×10^{-3}

[a] At 30 °C, $[Br_2]_0 = 5 \times 10^{-5}$ M, [KBr] = 0.1 M. Values of k_1^{calcd} were obtained from the least-squares analysis of k_1^{obsd} vs. ([uracil] − $[Br_2]_0$). [b] $[Br_2]_0 = 2.5 \times 10^{-5}$ M.

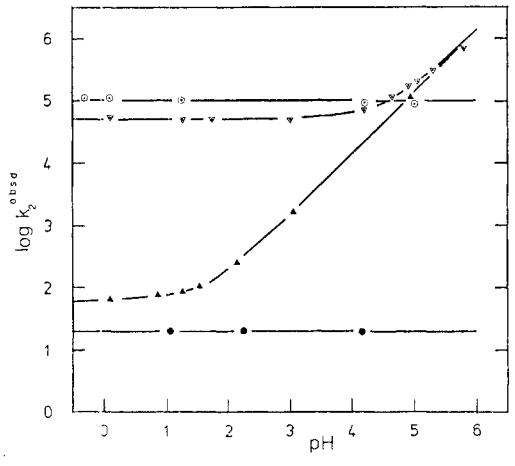


Figure 1. pH–rate profile for the reaction of bromine with uracils (1) and 5-bromouracils (3): ▽ for 1 ($R_1 = R_2 = H$), ⊙ for 1 ($R_1 = R_2 = Me$), ▲ for 3 ($R_1 = R_2 = H$), ● for 3 ($R_1 = R_2 = Me$). Data for 1 ($R_1 = H$, $R_2 = Me$) and 1 ($R_1 = Me$, $R_2 = H$) are very close to those for ▽ and ⊙ but are not shown in the interest of clarity.

methyluracil (1, $R_1 = R_2 = Me$), 5-bromouracil (3, $R_1 = R_2 = H$), and 5-bromo-1,3-dimethyluracil (3, $R_1 = R_2 = Me$) in aqueous media in the pH region 0–5 at 30 °C.

In the presence of a tenfold (or more) excess of the uracil substrate (1 or 3), the disappearance of bromine follows first-order kinetics (>90% reaction), and the derived rate constants (k_1^{obsd}) vary linearly with substrate concentration (Table I), indicating overall second-order behavior. In subsequent work, therefore, values of k_1^{obsd} were converted to second-order rate constants (k_2^{obsd}), taking into account the substrate concentration and the depletion of free bromine due to the formation of tribromide ion and hypobromous acid (see Experimental Section).

The values of k_2^{obsd} for the uracil substrates 1 at various pHs are listed in Table II, and some are depicted in Figure 1. The data observed for the 5-bromouracils 3 which were studied are presented in Table III and also depicted in Figure 1.

Over the whole pH range studied the rate constants for the reaction of bromine with the 1-methyl derivatives (1, $R_1 = Me$, $R_2 = H$ or Me; 3, $R_1 = R_2 = Me$) remain constant.[4] In contrast, the values for the derivatives bearing hydrogen at N_1 vary little at low pH but increase significantly at higher pH with a limiting slope of +1 for log k_2^{obsd} vs. pH (see Figure 1).

Table II. Acidity Dependence of Second-Order Rate Constants for Reaction of Bromine with Uracils 1[a]

R_1	R_2	pH	k_1^{obsd}, s^{-1}	$10^{-4} \times k_2^{obsd}$, $M^{-1}\ s^{-1}$	$10^{-4} \times k_2^{calcd}$, $M^{-1}\ s^{-1}$
H	H	0.11[b]	8.41	5.24	5.00
		1.24	8.00	4.99	5.00
		1.84	8.21	5.12	5.01
		3.00	7.79	4.86	5.13
		4.20	11.5	7.17	7.11
		4.64	17.5	10.9	10.8
		4.91	26.6	16.6	15.8
		5.05	32.1	20.0	19.9
		5.31	50.3	31.6	32.2
H	Me	1.26	10.4	6.48	6.47
		2.94	10.5	6.54	6.55
		4.34	13.5	8.41	8.42
		4.90	21.3	13.3	13.5
		5.01	25.0	15.6	15.6
Me	H	1.26	12.0	7.48	
		2.94	11.6	7.23	
		4.90	11.6	7.23	
Me	Me	−0.30[b]	17.9	11.2	
		0.11[b]	17.6	11.0	
		1.26	16.3	10.2	
		4.20	14.5	9.04	
		5.00	14.3	8.91	

[a] At 30 °C, [1] = 5.0×10^{-4} M, $[Br_2]_0 = 5.0 \times 10^{-5}$ M, and [KBr] = 0.1 M. Values of k_2^{calcd} from eq 2 and parameters in Table IV. [b] Value of H_0.

Table III. Acidity Dependence of Second-Order Rate Constants for Reaction of Bromine with 5-Bromouracils 3[a]

R_1	R_2	pH	k_1^{obsd}, s^{-1}	k_2^{obsd}, $M^{-1}\ s^{-1}$	k_2^{calcd}, $M^{-1}\ s^{-1}$
H	H	0.11[b]	0.0104	64.8	65.9
		0.89	0.0126	78.5	74.7
		1.26	0.0139	86.6	88.9
		1.52	0.0169	105	109
		1.73	0.0223	142	137
		2.13	0.0401	249	248
		3.05	0.256	1580	1590
		3.30	0.432	2780	2780
		4.95	18.4	115000	121000
Me	Me	1.03	0.00319	19.9	
		2.25	0.00322	20.1	
		4.15	0.00305	19.0	

[a] At 30 °C, [3] = 5.0×10^{-4} M, $[Br_2]_0 = 5.0 \times 10^{-5}$ M, and [KBr] = 0.1 M. Values of k_2^{calcd} from eq 2 and parameters in Table IV. [b] Values of H_0.

Discussion

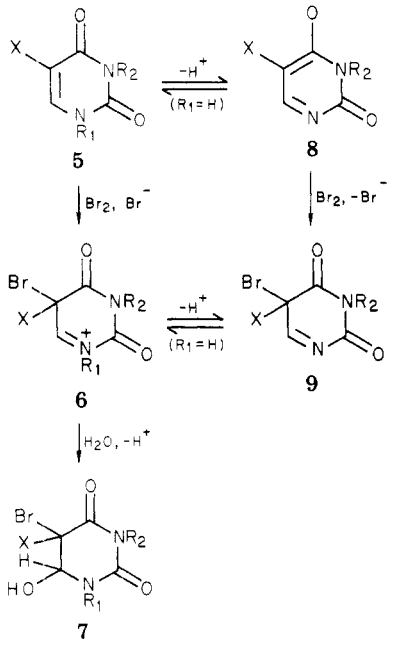
Electrophile. The active electrophile in these brominations is almost certainly molecular bromine (Br_2). Tribromide ion (Br_3^-), while present in a significant concentration, is a much weaker electrophile,[6] and even with

(4) The slightly higher values at the highest acidities probably reflect the fact that the ionic strengths of the sulfuric acid solutions rise above those of the buffer solutions (μ = 0.11 M).[5]

(5) O. S. Tee, D. C. Thackray, and C. G. Berks, *Can. J. Chem.*, **56**, 2970 (1978).

(6) (a) R. Taylor in "Comprehensive Chemical Kinetics", Vol. XIII, C. H. Bamford and C. F. H. Tipper, Eds., Elsevier, Amsterdam, 1972; (b) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", Elsevier, Amsterdam, 1965; (c) P. B. D. de la Mare, "Electrophilic Halogenation", Cambridge University Press, London, 1976.

Scheme II[a]

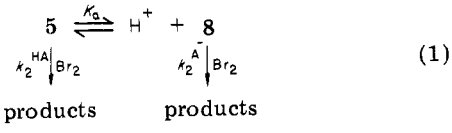


[a] X = H or Br; R_1 = H or Me; R_2 = H or Me.

highly reactive phenoxide ions its reactivity is only ~1% of that of Br_2.[7] Hypobromous acid (HOBr) is unlikely to be the electrophile since it is much less reactive than Br_2,[6] and its concentration is ≤1% of that of bromine under the experimental conditions. The more reactive protonated hypobromous acid (H_2OBr^+) or "positive bromine"[6] may be ruled out because of the lack of acid catalysis shown by the observed data.

Mechanism. Assuming then that the electrophile is Br_2, the results described above lead us to propose that the uracils employed in this study react with bromine by the mechanism shown in Scheme II. For 1-methyluracil, 1,3-dimethyluracil, and 5-bromo-1,3-dimethyluracil the invariance of k_2^{obsd} with pH is consistent with the simple pathway **5** + Br_2 → **6** → **7** (X = H or Br, R_1 = Me, R_2 = H or Me), where compounds **7** (X = H) are observable intermediates[1] and **7** (X = Br) are isolable products.[2]

The acidity dependences of k_2^{obsd} for uracil, 3-methyluracil, and 5-bromouracil have a form (see Figure 1) which suggests that at high acidity they also react by way of the pathway **5** + Br_2 → **6** → **7** but that at low acidity they react via their anions, i.e., **5** ⇄ **8** → **9** ⇄ **6** → **7**. The situation may be expressed by eq 1 which requires that the sec-



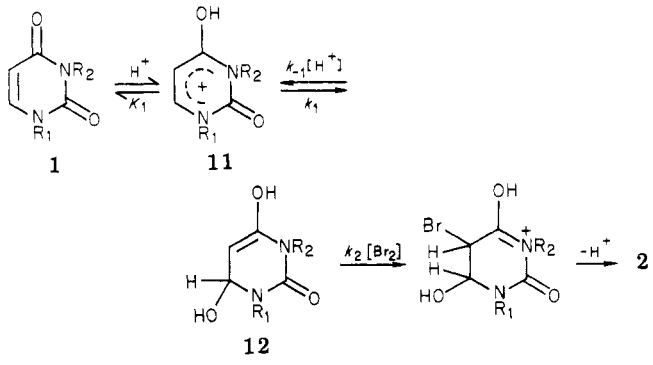
(1)

ond-order rate constants show an acidity dependence of the form shown in eq 2.

$$k_2^{obsd} = k_2^{HA} + k_2^{A^-}K_a/[H^+] \quad (2)$$

Equation 2 gives good fits to the observed data for uracil, 3-methyluracil, and 5-bromouracil, and the parameters obtained from the fitting (k_2^{HA} and $k_2^{A^-}K_a$ in Table IV) were used to calculate the values of k_2^{calcd} in Tables II and III and the curves in Figure 1. For comparative purposes

Scheme III



Scheme IV

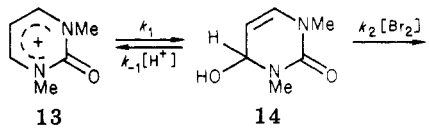
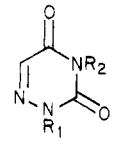


Table IV also contains the second-order rate constants for the 1-methyl analogues of these uracils and for the bromination of 6-azauracils **10** studied previously.[9]



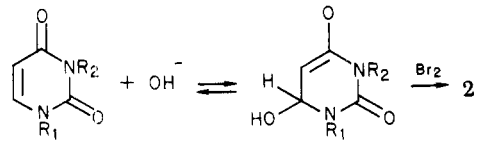
10, R_1 = H or Me; R_2 = H or Me

The values of k_2^{HA} for the attack of bromine upon the uracils **1** (R_1 = H, R_2 = H or Me) and upon **3** (R_1 = R_2 = H) are very similar to those observed for the 1-methyl analogues. This supports the notion that at low pH, when k_2^{HA} dominates eq 2, all of the substrates studied react via the pathway **5** + Br_2 → **6** → **7** (Scheme II).

At higher pH [>3 for uracils **1** (R_1 = H, R_2 = H or Me) and >1.5 for 5-bromouracil **3** (R_1 = R_2 = H)] the second term of eq 2 is dominant, corresponding to the reaction via the anions **8**. At first sight it may seem surprising that reaction via these anions is important in fairly acidic media. However, they are extremely reactive toward bromine ($k_2^{A^-} \approx 10^8$–10^{10} M^{-1} s^{-1}; see Table IV), and the uracils are easily deprotonated ($pK_a \approx$ 8–10). Similar behavior has been observed for various phenols,[7,10] and also, the much slower bromination of the 6-azauracils **10** (R_1 = H, R_2 = H or Me) probably occurs via their anions[9] (see Table IV). Furthermore, Santi and co-workers[11] have presented evidence that hydrogen–deuterium exchange of uracils **1** (R_1 = H, R_2 = H or Me) proceeds by way of their anions in basic media (pH 7–10) at 90 °C. Since bromine can be as much as 10^5–10^{14} times as reactive an electrophile as hydronium ion,[12] it is quite reasonable that bromination via the same anions is operative at pH >3.

(7) R. P. Bell and D. J. Rawlinson, *J. Chem. Soc.*, 63 (1961).
(8) D. J. Brown, *Chem. Heterocycl. Comp.*, **16** (1962); *Suppl. 1* (1970).
(9) S. Banerjee and O. S. Tee, *J. Org. Chem.*, **41**, 4004 (1976).
(10) J. Kulic and M. Vecera, *Collect. Czech. Chem. Commun.*, **39**, 171 (1974).
(11) D. V. Santi, C. F. Brewer, and D. Farber, *J. Heterocycl. Chem.*, **7**, 903 (1970).
(12) Bromine is 10^5 times as reactive as H_3O^+ toward the very reactive enol of acetone;[13] toward much less reactive styrene it is 10^{14} times as reactive[14] (all reactions in water at 25 °C).
(13) J. E. Dubois and J. Toullec, *J. Chim. Phys. Phys.-Chim. Biol.*, **65**, 2166 (1968); *J. Chem. Soc., Chem. Commun.*, 478 (1969).
(14) R. Bolton in "Comprehensive Chemical Kinetics", Vol. IX, C. H. Bamford and C. F. H. Tipper, Eds., Elsevier, Amsterdam, 1973; M. F. Ruasse and J. E. Dubois, *J. Am. Chem. Soc.*, **97**, 1977 (1975).

Scheme V



Alternative Mechanisms. We have considered the viability of other mechanisms in relation to the observed data. An attractive alternative route to the observable intermediate **2** involves attachment of the hydroxyl at C_6 prior to the attack of bromine at C_5 (Scheme III). This route is attractive since the cation **13** is known to react via the pseudobase **14** (Scheme IV).[5] Furthermore the cation **11** is the accepted[15] protonated form ($pK_1 \simeq -3.3$)[16] of the uracils **1**, and the enol/enamine **12** should be extremely reactive toward bromine.[17] The mechanism set out in Scheme III might account for the acid-invariant rate constants for **1** (R_1 = Me, R_2 = H or Me) and the values of k_2^{obsd} at low pH obtained for **1** (R_1 = H, R_2 = H or Me). However, this may be ruled out as follows.

Assuming a steady-state concentration of the very reactive[17] intermediate **12**, and for $[H^+] \ll K_1 \simeq 10^{3.3}$, one may derive eq 3 for Scheme III. For this equation to be

$$\text{rate} = \frac{k_1 k_2 [1][H^+][Br_2]}{k_{-1}[H^+] + k_2[Br_2]} \quad (3)$$

compatible with the observed second-order behavior and lack of acidity dependence, it is required that $k_{-1}[H^+] \gg k_2[Br_2]$. In this case eq 3 simplifies and

$$k_2^{obsd} = k_1 k_2 / K_1 k_{-1} \quad (4)$$

The attack of bromine upon **12** would almost certainly be diffusion controlled ($k_2 \simeq 10^{10}$ M^{-1} s^{-1}).[17] Therefore, for $[Br_2] \leq 5 \times 10^{-5}$ M and $[H^+]$ as low as 10^{-5} M, the above inequality implies that $k_{-1} \gg 5 \times 10^{10}$ M^{-1} s^{-1}. Likewise, $k_2^{obsd} \approx 10^5$ M^{-1} s^{-1}, and eq 4 requires $k_1/k_{-1} \approx 0.02$ M and $k_1 \gg 10^9$ s^{-1}. These values of k_1 and k_{-1} are not reasonable. For the closely related structure **14** the corresponding values[5] are much lower at $k_1 = 1.5$ s^{-1} and $k_{-1} = 2 \times 10^7$ M^{-1} s^{-1}. On this basis we can safely rule out the mechanism in Scheme III.

An alternative mechanism to explain the pH dependence of eq 2 could be that shown in Scheme V. A similar mechanism has been proposed for the base-catalyzed H–D exchange of 1-methyluracils.[11] Consideration of Scheme V in terms of the observed data, along the same lines as that given above for Scheme III, also leads to unreasonable requirements for the rate constants for the formation and decomposition of the enolate **15**.[19] A further point which militates against Scheme V is lack of observation of a comparable pH-dependent bromination of 1-methyluracils. If Scheme V were operating for **1** (R_1 = H), one would expect it to be operating for **1** (R_1 = Me) also, albeit perhaps somewhat slower.

Similar considerations preclude the operation of mechanisms analogous to those of Schemes III and V applying to the bromination of the 5-bromouracils **3**.

In principle uracil could react with bromine by way of some tautomer other than the diketo structure **1** ($R_1 = R_2$ = H) depicted.[15] However, in view of the similar pH-independent rate constants (k_2^{HA} in Table IV) for all the uracils **1** (R_1 = H or Me, R_2 = H or Me), it is most reasonable that it reacts as the tautomer **1** ($R_1 = R_2$ = H) shown. A similar argument can be made that 5-bromouracil reacts as the tautomer **3** ($R_1 = R_2$ = H) at low pH.

Relative Reactivities. The rate constants (Table IV) ascribed to the substrates studied on the basis of the mechanism depicted in Scheme II appear to us to be quite reasonable. However, before supporting this assertion, we consider more fully the value of $k_2^{A^-}$ appropriate to the uracil anion **8** (X = H, R_2 = H).

The literature[21] pK_a (=9.46) for uracil applies to ionization of the N_3–H bond.[15,21] Since the pK_as for 1-methyluracil and 3-methyluracil are 9.74 and 9.95, respectively,[22] it is likely that the pK_a for ionization of the N_1–H bond of uracil is ~9.65. In this case $k_2^{A^-} \approx 6 \times 10^9$ M^{-1} s^{-1} rather than 4×10^9 M^{-1} s^{-1} which would correspond to a pK_a = 9.46.

The value of k_2^{HA} for uracil is similar to that for phenol (1.8×10^5 M^{-1} s^{-1}).[7] Likewise, the $k_2^{A^-}$ value for the uracil anion is of the same order as those for simple phenoxide ions (10^9–10^{10} M^{-1} s^{-1}) and is close to diffusion controlled.[7,10] Uracil is 800 times more reactive than 5-bromouracil, whereas phenol is only 56 times as reactive as *p*-bromophenol.[7,23] This difference may be due to the fact bromine attacks ipso to the 5-bromo substituent of **3** but meta to the *p*-bromo substituent of *p*-bromophenol.

A more meaningful comparison is that between the 1,3-dimethyluracils **16** and the closely related pseudobases **17** and **18** shown in Table V. In the case of the 1,3-dimethyluracils **16** the presence of a 5-bromo substituent causes a rate reduction of 5000 whereas for the more reactive pseudobase **17** it causes a reduction of 500. This is perhaps a manifestation of the reactivity–selectivity principle.[26] Also note from Table V that the carbonyls of **16** (X = H) reduce the reactivity of **17** (X = H) and **18** (X = H) by (2–3) $\times 10^4$, which is reasonable.

From Table IV we may also note the large deactivation brought about by a 6-aza nitrogen. For uracil it is 4×10^7 and for 1,3-dimethyluracil it appears to be ~10^9. The earlier estimate[9] of 10^{10} did not take into account the contribution of the uracil anion mechanism.

(15) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles", Academic Press, New York, 1976.
(16) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962).
(17) Bromine reacts with the enol of acetone at a diffusion-controlled rate[18] and with **14** (Scheme IV) with $k_2 \simeq 2 \times 10^9$ M^{-1} s^{-1}.[5] Therefore, **12**, which has the structural features of both of these substrates, should also react at a diffusion-controlled rate ($k_2 \approx 10^{10}$ M^{-1} s^{-1}).
(18) J. E. Dubois and J. Toullec, *Tetrahedron*, **29**, 2859 (1973).
(19) On the other hand a comparable analysis of the anion mechanism $5 \rightleftarrows 8 \xrightarrow{Br_2} 9$ leads to rate constants for the formation and reprotonation of the anion **8** (X = H) very close to those actually observed.[20]
(20) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(21) J. J. Christiansen, J. H. Rytting, and R. M. Izatt, *J. Phys. Chem.*, 71, 2700 (1967).
(22) Averages of the values given by Brown.[8]
(23) The value of k_2^{HA} for *p*-bromophenol given in ref 7 is in error. It should be 3.2×10^8 M^{-1} s^{-1}. R. P. Bell, personal communication.
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(27) By way of comparison, a similar plot for phenols and phenoxides would have a slope of ~1.5 (from the ratio of ρ_m values[10] for these substrates).
(28) H. M. Gilow and J. H. Ridd, *J. Org. Chem.*, **39**, 3481 (1974).
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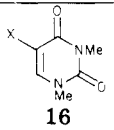
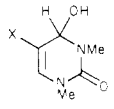
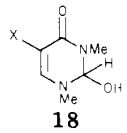
(32) J. M. Pink, *Can. J. Chem.*, **48**, 1169 (1970). This value is for 25 °C and is probably not very different at 30 °C. Since the correction for HOBr which is later applied is only of the order of a few percent, the temperature difference is ignored.

Table IV. Kinetic Parameters for Reaction of Bromine with Uracils[a]

uracil	pK_a	k_2^{HA}, M^{-1} s^{-1}	$k_2^{A^-}K_a$, s^{-1}	$k_2^{A^-}$, M^{-1} s^{-1}
1 (R_1 = R_2 = H)	~9.65[b]	5.00×10^4	1.33	$\sim 6 \times 10^9$[b]
1 (R_1 = H, R_2 = Me)	9.95	6.47×10^4	0.89	7.9×10^9
1 (R_1 = Me, R_2 = H)	9.75	7.2×10^4		
1 (R_1 = R_2 = Me)		10×10^4		
3 (R_1 = R_2 = H)	8.0	64	1.36	1.4×10^8
3 (R_1 = R_2 = Me)		20		
10 (R_1 = R_2 = H)	9.5	12×10^{-4}	2.2×10^{-4}	7×10^5
10 (R_1 = H, R_2 = Me)	9.52	5.6×10^{-4}	3.5×10^{-4}	12×10^5
10 (R_1 = R_2 = Me)		$\sim 1 \times 10^{-4}$		

[a] Data for 10 from ref 9. pK_as from ref 8 and 21. [b] See Discussion in text.

Table V. Second-Order Rate Constants for Reaction of Bromine with Tetrahydropyrimidinones[a]

structure	k_2, M^{-1} s^{-1} X = H	X = Br	ref
 16	10^5	20	this work
 17	2×10^9	4×10^6	5, 24
 18	3×10^9		25

[a] At 30 °C.

The values of k_2^{HA} for the various uracils vary over a range of 10^8 while the range of $k_2^{A^-}$ is only 10^4 (Table IV). Thus the substituent effects are less pronounced for the more reactive anions, a further example where the reactivity–selectivity principle[26] appears to work. Also, the substituent effects for the 5-bromo and 6-aza substituents seem to be regular, and a plot of log k_2^{HA} vs. log $k_2^{A^-}$ gives a good straight line of slope 2.0 for **1**, **3**, and **10** (R_1 = R_2 = H).[27]

The effect of *N*-methyl groups upon the reactivity of the uracils in Table IV is variable, leading in some cases to a small increase and in others to a small decrease. This variability is not unusual and has been observed in various systems involving *N*-methyl and *O*-methyl substitution.[6a,7,28]

Conclusions

The results of our kinetic study of the reaction of bromine with the uracils **1** and **3** are explicable by the mechanism set out in Scheme II. Substrates bearing a methyl group at N_1 (i.e., **5**, R_1 = Me) are constrained to react by the pathway **5** → **6** → **7**. Substrates with a hydrogen at N_1 (**5**, R_1 = H) also employ this pathway at high acidity, but at lower acidities reaction via the anions **8** becomes predominant.

Together with the results of an earlier study[1] on the conversion of the intermediates **2** to 5-bromouracils **3**, the present findings provide mechanistic details for the overall electrophilic substitution **1** → **2** → **3** and for the addition **3** → **4**. However, they do not resolve the dichotomy shown by uracils in titration with bromine at low acidity whereby uracils **1** (R_1 = Me) show a 1:1 reaction and uracils **1** (R_1 = H) show a 1:2 reaction.[1] Although, as shown here, 5-bromouracil **3** (R_1 = R_2 = H) reacts rapidly with bromine at low acidity, the conversion **2** → **3** is too slow[1] to account for the 1:2 reaction.

Experimental Section

Uracil and 1,3-dimethyluracil were of commercial origin. The remaining substrates were prepared by literature methods: 1-methyluracil,[29] 3-methyluracil,[30] 5-bromouracil,[2] 5-bromo-1,3-dimethyluracil.[2] All substrates were recrystallized before being used. The acidic media and the bromine solutions used in kinetic experiments were as described in another recent study.[5]

All kinetic solutions were 0.1 M in potassium bromide. The use of this large concentration of bromide ion has several advantages. First, it swamps the effect of bromide ion produced by the reaction. Second, it enhances the stability of the bromine solutions since much of the bromine is present as tribromide ion (Br_3^-). Third, it reduces the rate of reaction by reducing the free bromine concentration. Fourth, it facilitates spectrophotometric measurement of rates since Br_3^- has a larger extinction coefficient than Br_2 at their respective λ_{max}. Fifth, it means that the ionic strength was high and constant at 0.11 M for all experiments carried out in buffer solutions (0.01 M deriving from the buffer components).[5]

Kinetic experiments were largely carried out by using the apparatus previously described.[5] Bromine disappearance was measured by using the decrease in absorbance due to Br_3^- in the region 280–320 nm relative to the little or no change occurring at 350 nm. Initially, absorbance vs. time was recorded on an HP 141A storage oscilliscope and, the traces were photographed with an HP 197A Polaroid camera. Later on use was made of a Biomation 805 waveform recorder as described elsewhere.[5] Some of the reactions of 5-bromouracil were sufficiently slow that absorbance changes were monitored on the X-Y recorder of the spectrophotometer. The reactions of the 5-bromo-1,3-dimethyluracil were so slow that they were followed by conventional means.

Pseudo-first-order rate constants (k_1^{obsd}) were obtained from least-squares analysis of ln ($A - A_\infty$) vs. time ($r \geq 0.9995$), covering ~90% reaction. Each k_1^{obsd} in the text is the average of several (usually four) runs. Apparent second-order rate constants were calculated from $k_2^{app} = k_1^{obsd}/([\text{uracil}] - [Br_2]_0)$ for reasons discussed earlier.[24] The second-order rate constants (k_2^{obsd}) in the text were obtained from $k_2^{obsd} = k_2^{app}[Br_2]_s/[Br_2]$, which takes account of the difference between the stoichiometric concentration of bromine, $[Br_2]_s$, and the concentration of free bromine, $[Br_2]$. These concentrations differ because of the formation of tribromide ion and, at higher pH, of hypobromous acid.

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

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

That is, $[Br_2]_s = [Br_2] + [Br_3^-] + [HOBr]$. Thus from $K_1 = [Br_2][Br^-]/[Br_3^-]$ (=0.0554 M)[31] and $K_2 = [H^+][Br^-][HOBr]/[Br_2]$ (=9.6×10^{-9} M^2)[32] one can derive eq 5, since both $[Br^-]$ and $[H^+]$

$$\frac{[Br_2]_s}{[Br_2]} = 1 + \frac{[Br^-]}{K_1} + \frac{K_2}{[H^+][Br^-]} \quad (5)$$

remain constant throughout the reaction. The last term of eq

5 is only significant (>0.01) at pH >5 under our conditions ([Br^-] = 0.1 M).

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Registry No. 1 (R_1 = R_2 = H), 66-22-8; 1 (R_1 = R_2 = Me), 874-44-6; 1 (R_1 = H, R_2 = Me), 608-34-4; 1 (R_1 = Me, R_2 = H), 615-77-0; 3 (R_1 = R_2 = H), 51-20-7; 3 (R_1 = R_2 = Me), 7033-39-8; 10 (R_1 = R_2 = H), 461-89-2; 10 (R_1 = H, R_2 = Me), 1627-30-1; 10 (R_1 = R_2 = Me), 15677-10-8.

Zwitterion Cycloadditions and Free-Radical Polymerizations of *p*-(Dimethylamino)styrene with Tris- and Tetrakis(carbomethoxy)ethylenes

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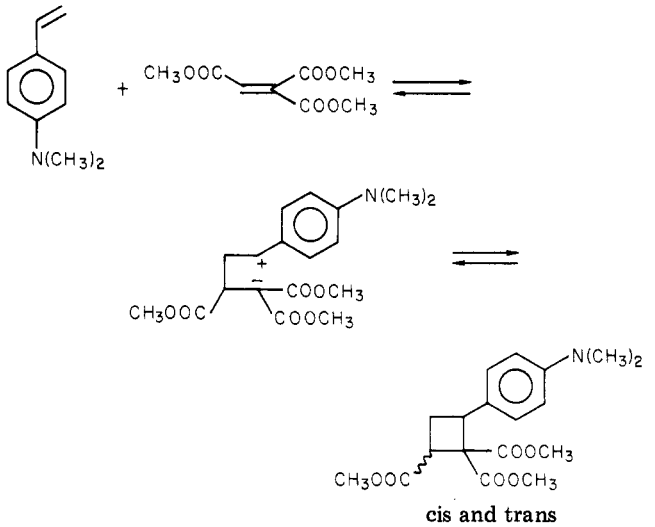
Tris- and tetrakis(carbomethoxy)ethylenes reacted with *p*-(dimethylamino)styrene to form cyclobutane cycloadducts. The reaction proceeded faster in polar solvents than in nonpolar solvents. This evidence supports a zwitterion intermediate in the cycloaddition reaction, but an intermediate could not be trapped with methanol, acetonitrile, or phenyl isocyanate. The cycloaddition reaction was not influenced by UV irradiation, radical inhibitors, or the one-electron oxidant ferric nitrate. These results are evidence against a possible cation-radical intermediate. Free-radical-initiated copolymerization occurred between tris- but not tetrakis(carboxymethoxy)ethylene and *p*-(dimethylamino)styrene to yield approximately alternating copolymers. These data are completely analogous to those obtained with other electron-rich styrenes and electrophilic trisubstituted ethylenes.

Both cycloaddition and polymerization reactions of electron-rich olefins with electron-poor olefins have been widely studied. Tetracyanoethylene has been known for a long time to react with olefins with a strongly electron-donating substituent, such as vinyl ethers, vinyl sulfides, vinylamines, and styrenes with electron-donating substituents in the para position.[1-4] Huisgen has extensively studied the reaction of tetracyanoethylene with vinyl ethers.[5-9] In this laboratory, the reaction of electron-deficient trisubstituted olefins such as tricyanoethylene with electron-rich olefins such as enamines and vinyl ethers has been studied.[10] These cyclobutane derivatives are mostly believed to arise from initial formation of a 1,4-zwitterion intermediate.

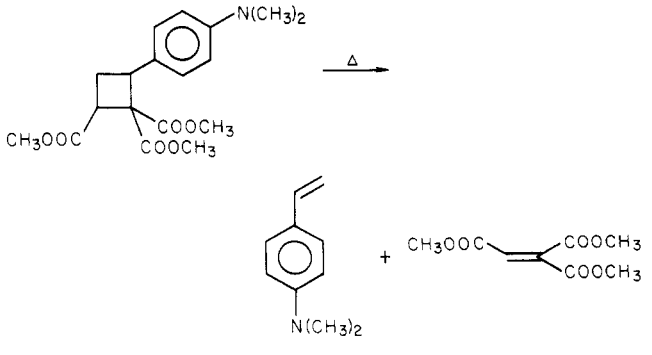
Regarding the polymerization reactions, neither tri- nor tetrasubstituted electrophilic ethylenes have been homopolymerized. Using free-radical initiations, the tri- but not the tetrasubstituted ethylenes smoothly copolymerize with electron-rich ethylenes to form 1:1 alternating copolymers.[11]

Recently, the highly electron-rich olefin *N*-vinylcarbazole was found to add to electrophilic ethylenes by a cation-radical route.[12] Accordingly, it was of interest to examine the still more electron-rich olefin *p*-(dimethylamino)-styrene in cycloaddition and copolymerization reactions.

Scheme I



Scheme II



Results and Discussion

Intermediates. *p*-(Dimethylamino)styrene was prepared from the Grignard reaction of *p*-(dimethylamino)-benzaldehyde and methyl iodide, followed by dehydration

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