Reinvestigation of the Mechanism of Bromination of Uracil and its *N*-Methyl Derivatives

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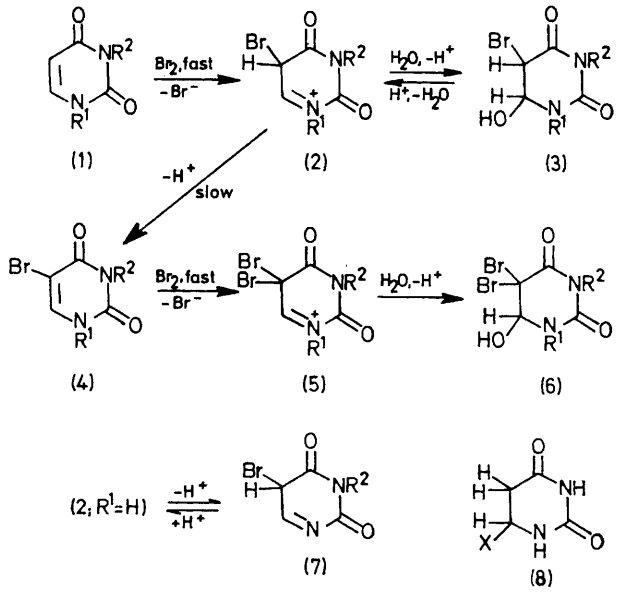
Summary Uracils bearing substituents at N_1 react rapidly with bromine in aqueous acidic solutions to give "HOBr" addition products, which undergo slow acid-catalysed dehydration to 5-bromo-uracils (**4**). Uracils bearing only hydrogen at N^1 react rapidly with bromine to give sequentially (**4**) and then the 5,5-dibromo-derivatives (**6**). This rapid reaction is suppressed, however, in strong acid, where N^1 of the intermediate (**7**) may be protonated. Mechanisms to accommodate these observations are suggested, including one involving a transient *N*-bromo species (**2**; R^1 = Br).

THE tendency of uracils (**1**) to undergo addition reactions may have important biological consequences.[1] Well documented is the photochemically induced addition of water to uracil to give (**8**; X = OH),[2] and the thermal addition of $NaHSO_3$ to give (**8**; X = SO_3Na).[3] Moreover, the bromination of uracil is believed to involve addition processes. Wang[4] suggested that attack by bromine upon uracils is rapid and leads to the adducts (**3**) which subsequently undergo elimination to the 5-bromo-uracils (**4**). These in turn react further with bromine to give isolable adducts (**6**). Other workers,[5] however, found that spectrophotometric and potentiometric titration of 1,3-dimethyl-



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uracil (**1**; $R^1 = R^2 = Me$) and of uridine (**1**; R^1 = ribosyl, $R^2 = H$) with bromine in a buffer of pH = 4·76 implicate a rapid 1 : 1 reaction, whereas uracil (**1**; $R^1 = R^2 = H$) reacts rapidly with 2 mol. equiv. of bromine to give the 5,5-dibromo-derivative (**6**; $R^1 = R^2 = H$). We report here our preliminary findings on the bromination of uracils, and suggest a reason for the two types of behaviour first evident in the work of Moore and Anderson.[5]

accompanied by shifts to longer wavelengths as well as by a decrease in absorbance, suggesting the *rapid* formation of 5-bromo-3-methyluracil (**4**; $R^1 = H$, $R^2 = Me$), and the simultaneous bromination of 3-methyluracil and 5-bromo-3-methyluracil. In the stronger acid, however, both uracil and 3-methyluracil react only with 1 mol. equiv. of bromine, and no shift in wavelength is apparent, *i.e.* we are again observing simply (**1**) → (**3**). It seems, therefore, that

TABLE 1

Rate of appearance of the 5-bromo-uracils (**4**) from the adducts (**3**).

	$k_{obs} \times 10^4$ min^{-1}			
$[H_2SO_4]$/N	$R^1=R_2=H$	$R^1=H$, $R^2=Me$	$R^1=Me$, $R^2=H$	$R^1=R^2=Me$
0·5	8·61	16·8	4·98	9·07
1·0	11·5	26·4	11·1	21·8
2·0	21·1	56·1	32·9	71·6
4·0	58·8	177	154	371
4·0	13·6[a]	—	—	105[a]

[a] Refer to the 5-deuterio-substrates.

The adducts (**3**) are readily characterised by ^1H n.m.r. spectroscopy, and show two well resolved doublets in the region δ 4·30—5·40 for 5- and 6-H. These absorptions slowly disappear, and are replaced by peaks appropriate to (**4**). In other experiments we have measured spectrophotometrically the rate of appearance of the 5-bromo-uracils (**4**) in aqueous sulphuric acid solutions. The pseudo-first-order rate constants observed (Table 1) are independent of initial bromine concentration, but are markedly dependent upon the acidity. The similarity of the rate data for the four substrates (**1**; R^1 = H or Me, R^2 = H or Me), and the observation of sizable isotope effects (k_H/k_D = 4·3, 3·5) for the 5-deuterio-derivatives of (**1**; $R^1 = R^2 = H$, or $R^1 = R^2 = Me$) suggests that all four 5-bromo-uracils (**4**; R^1 = H,Me; R^2 = H,Me) are formed by a rate-determining dehydration (**3**) ⇌ (**2**) → (**4**). A similar mechanism is operative in the bromination of pyrimidin-2(1*H*)-one and its derivatives.[6]

It appears therefore that, in the absence of excess of bromine, the uracils (**1**) undergo monobromination *via* the addition–elimination sequence (**1**) → (**3**) → (**4**), as Wang suggested.[4] However, since the conversion (**3**) → (**4**) is *slow*, this scheme does not account for the *rapid* formation of the dibromo-derivative (**6**; $R^1 = R^2 = H$) during the titration of uracil with bromine.[5] We have now studied the spectrophotometric titration of uracils with bromine in both strongly and weakly acidic media (see Table 2). For the N^1-substituted uracils the long wavelength absorptions smoothly collapse upon addition of bromine. On the other hand, 3-methyluracil (**1**; $R^1 = H$, $R^2 = Me$) behaves like uracil[5] in that stepwise addition of bromine in weak acid is where N^1 of the uracil ring is substituted, or in strong acids where N^1 in some intermediate may be protonated, rapid formation of 5-bromo-uracils is suppressed.

TABLE 2

Spectrophotometric titrations of uracils with bromine.

Uracil (**1**)	Uracil : bromine	
	0·1N-H_2SO_4	4·0N-H_2SO_4
$R^1 = R^2 = H$	1 : 2	1 : 1
$R^1 = H$, $R^2 = Me$	1 : 2	1 : 1
$R^1 = Me$, $R^2 = H$	1 : 1	—
$R^1 = R^2 = Me$	1 : 1	—
R^1 = ribosyl, $R^2 = H$ ..	1 : 1[a]	—

[a] From ref. 5, in buffer of pH 4·76.

In explanation we suggest that in solutions of low acidity the intermediate ion (**2**; $R^1 = H$, R^2 = H or Me) is in equilibrium with its conjugate base (**7**; R^2 = H or Me) which may be rapidly converted into (**4**; $R^1 = H$, R^2 = H or Me) by interaction with bromine. This may occur *via* the formation of an *N*-bromo-derivative (**2**; $R^1 = Br$) which undergoes rapid deprotonation at C-5 to give (**4**; $R^1 = Br$) and then (**4**; $R^1 = H$) which then reacts rapidly with bromine to give (**6**; $R^1 = H$). Such a mechanism would be suppressed in strong acid if the equilibrium between (**2**; $R^1 = H$) and (**7**) greatly favours (**2**). Moreover this mechanism is impossible if in (**2**), R^1 = Me or ribosyl.

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