MECHANISMS OF AQUEOUS BROMINATION OF PYRIMIDONES, PYRIDONES, AND PHENOLS

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ABSTRACT

Mechanisms of Aqueous Bromination of Pyrimidones, Pyridones, and Phenols

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The kinetics of bromination of pyrimidone, pyridones, and phenols were measured in aqueous solution by stopped-flow UV spectroscopy. Mechanistic conclusions were drawn for each of the three classes of compounds as to the probable form of the reactive species.

The results for 2- and 4-pyrimidone are consistent with bromination of their covalent hydrates at pH < 4 and their anions at pH > 4. The monomethyl derivatives of 2- and 4-pyrimidone apparently react via their covalent hydrates at pH < 5 and via their free-bases at pH > 5. The 1,3-dimethyl derivatives of the parent pyrimidones brominate via their pseudobases, a conclusion supported by kinetic studies of the equilibration of these quaternary cations and their pseudobases. The analogy between reaction via covalent hydrates and via pseudobases has permitted estimates of the extent of covalent hydration of 2- and 4-pyrimidone in water.

The free-base (lactam) form of the pyridones (2- and 4-) appear to be the reactive species at pH < 5. The pH-rate data indicate reaction

via their anions at pH > 5. That the lactam tautomer is the reactive form at low pH is supported by the similar reactivity of the N-methyl pyridones. Related studies of the monobromo derivatives reveal the origin of the facile dibromination of pyridones and permit choice of conditions to achieve useful monobromination.

The polybromination of phenol and 4-bromophenol was studied. The results have been discussed by comparing the kinetics of bromination of phenol, 2-bromo-, 4-bromo-, 2,4-dibromo-, and 2,6-dibromophenol under pseudo-first-order conditions (excess substrate). Depending upon the pH each of these reacts via its free-acid form or via its anion.

Bromination of all the above compounds leads to multiple substitution. Product studies (GC, UV, and NMR) were carried out to obtain product ratios and hence partial rate factors. With the latter the behaviour of the phenols and their anions could be correlated with Hammett substituent constants. It is also possible to include pyridones, pyrimidones, and their anions in such correlations.

Various types of kinetic behaviour were observed: zero-order, first-order, second-order, and mixed orders. Approaches to analyzing these are discussed, as well as ways to handle consecutive second-order processes such as found for the phenols and the pyridones.

To my Parents

and my Loving Wife

"We make our own world when we have made it awry, we can remake it, approximately truer, though it cannot be absolutely true, to the facts."

HAVELOCK ELLIS

ACKNOWLEDGEMENTS

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Commendable is the work of the Faculty of Chemistry at Concordia for teaching a science in which I was very ignorant.

Recognition is also due to my schoolfellows for preserving a family ambiance.

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GENERAL INTRODUCTION

Derivatives of pyrimidines and pyrimidones are the fundamental building blocks of nucleic acids. As a consequence much research on their synthesis and structure has been carried out.[1] Studies on their reactivity, mechanism, and tautomerism are invaluable in understanding the role that these nitrogen heterocycles may play in many biochemical processes such as proton transport, enzymatic catalysis, and spontaneous or induced mutations.[2]

Interest in these compounds, as well as in the pyridines, has shifted from theoretical to practical application. Interferon, the purported new "wonder drug"[3] is an effective antiviral and antineoplastic agent at subnanogram level, but it is very difficult to produce and purify. Recent experiments have shown that 5-halopyrimidones can induce interferon in vivo in several species, and in vitro in mammalian cell culture, including human cells.[4,5]

Halopyridones, on the other hand, have found different utility in medicinal chemistry. For example, derivatives of 2-(1H)-pyridones were found to have antiinflammatory and antipyrectic activity when tested orally in rats.[6] Diiodo-4-pyridones have been used as radiopaques or contrast media for visualization of body organs or cavities.[7] While the sodium salt of 5-iodo-2-oxo-pyridine, 1-methyl-5-iodo-2(1H)-pyridone,

and the sodium salt of 5-iodo-2-oxo-1(2H)-pyridine acetic acid have been used as X-ray contrast agents.[8]

Phenols are important industrial substrates for the manufacture of polymers. Even so phenol and polyphenols may be used as molecular models to investigate the nature of the interaction of more complex biological structures having these moieties (catecholamines, tannins, thyroid hormones, etc.) with other systems such as NAD+, nucleic-acid bases, proteins etc.[9] The phenolic aromatic ring and, in particular, the presence of functional groups capable of forming intra-molecular hydrogen bonds appear to be structural necessities for pharmacological activity.[9] Thus, many materials that man uses contains phenolics: pesticides and disinfectants, drugs, preservatives,[9] wine,[10] and beer.[11] Furthermore, when large amounts of phenolic wastes from pulp and paper industries and from pesticides are dumped in waters, ecological problems arise. Therefore, the halogenation or dehalogenation of these phenolic compounds has potential relevance to their effect on biological organisms.

Such stimulus has prompted the study of the mechanisms of bromination of pyrimidones, pyridones, and phenols which are the subject of this thesis. The above substrates have two, one and no aza nitrogens respectively, and such a kinetic study should enable a correlation of the effect of the ring nitrogens upon the electrophilic substitution reaction. Identification of the intermediates,[17b,18,19,95] and analysis of their decay kinetics as a function of acidity, leads to the formulation of the individual reaction schemes. In some instances, depending upon the reaction conditions, the ratio of monobromo products

were unexpected. Thus, an assessment of the role of the functional groups is imperative to allow for mechanistic correlations to be made within the systems with the same number of aza nitrogens, and correlation between systems with different aza nitrogens.

Although much of the author's research work has already been published[17,95] or presented in various colloquia and symposia, this thesis retains the style of an original work. In addition to presenting all the kinetic data, it contains an ample discussion of mechanisms with additional unpublished data supporting more elaborate pathways, and documents in greater detail the synthetic reactions and product studies performed. For clarity of presentation a division into chapters was implemented. The first three discuss the kinetics of bromination of the individual classes of compounds: the pyrimidones, the pyridones, and the phenols, reflecting the chronology in which the studies were done. The fourth chapter concatenates these three systems using the Hammett plots as a basis for discussion.

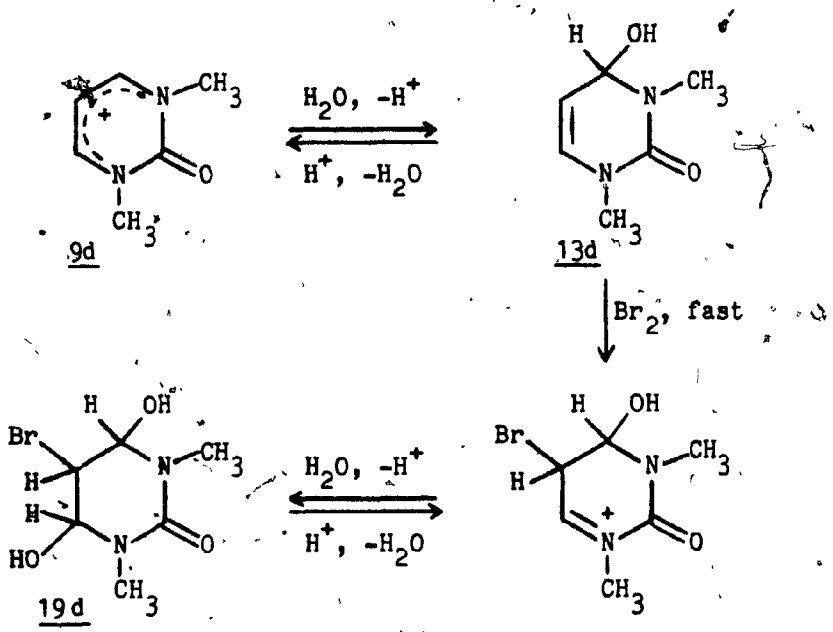
I. THE PYRIMIDONES

The covalent addition of water or hydroxide across the C=N bond of π-deficient heterocycles has been proposed, in earlier literature, as being responsible for peculiar spectroscopic,[13] synthetic,[38,49] and kinetic[17a,b,18,19] behaviour of the pyrimidones. Although the subject of pseudobases has been reviewed,[14-16] scarce first-hand data are available to show the existence and involvement of covalent hydrates in various reactions. Interpretation of the data is complicated by an additional pre-equilibrium protonation of the pyrimidone and a very low equilibrium concentration of the covalent hydrate. However, useful results can be obtained by indirect kinetic methods, as will be shown in this chapter.

Earlier work in this laboratory has shown the involvement of long-lived intermediates in the aqueous bromination of mono- and dioxo-pyrimidines: 2-pyrimidones,[18a,b,d] 4-pyrimidones,[18c] uracils,[18e] and cytosines.[49b] These intermediates could arise from attack of bromine, followed by the capture of water, or vice versa. Recent work, including the present, has sought to differentiate between these two possibilities.

The formation of the intermediates is too fast to be studied by conventional means. However, by the use of the stopped-flow method

these processes can be studied. Berks was able to show that for uracils[49a] and for cytosines[49b] the intermediates arise by bromine attack, followed by the attack of water. In contrast, Berks and Thackray[19] showed that the intermediate 19d, observed[18a] in the bromination of the cation 9d, arises by the attack of bromine upon the pseudobase 13d.



Depending upon the pH, either the attack of bromine (pH < 2) or the formation of the pseudobase (pH > 3) is rate-limiting.[19] A separate study of the kinetics of equilibration of the cation 9d and its pseudobase fully supported this interpretation.[19]

The work of Berks and Thackray[19] was the immediate precursor to the present study of the bromination of 2-pyrimidone and 4-pyrimidone. It established the utility of the stopped-flow method for monitoring the fast bromination step and indicated that a change of rate-determining step (with pH) could be anticipated if the covalent hydrate of these

substrates were involved. Such was found to be the case, as is documented below.

The results of bromination of 2- and 4-pyrimidones and derivatives, reported in this chapter, serve to emphasize the existence of covalent hydrates, estimate their quantity in water, and show the dramatic effect that they can have on reactivity. It may appear, for more complex kinetics, that legerdemain was employed in extracting the rate constants from the data. However, the experimental traces soundly justify the use of equations for reactions occurring via mixed-order pathways. At certain pHs, the complexity increases due to the concomitant reaction of different forms of the substrate. These were mathematically extricated from a competitive mechanism in which only one reactive form becomes dominant at the extrema of the pH range. Catalytic and equilibration constants closely agree with those of the kinetics of bromination corroborating further the overall mechanism and equations presented. Moreover, the predominance of tautomeric ratios (lactam/lactim, α-lactam/γ-lactam) for 2- and 4-pyrimidones can be inferred from the rate profiles and reactivities of the N-methyl analogues.

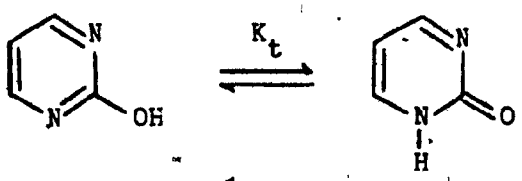
STRUCTURE OF THE PYRIMIDONES

The electronic structures of the derivatives of pyrimidine and pyridine have been extensively studied by many investigators.[20,21] In particular some of these compounds such as uracils, cytosine, thymine,

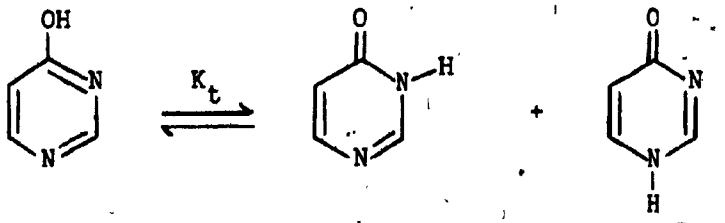
and vitamin B_6, have attracted special interest because of their biological importance.

Considerable attention has been paid to the problem of tautomerism between lactam and lactim forms, which can be expected in these heterocyclic compounds because of the presence of labile hydrogens atoms. The pivotal role which prototropic equilibria plays in the action of numerous therapeutic agents has been thoroughly documented.[22] Therefore the ability to predict quantitatively one of the thermodynamic parameters connected with these events would be particularly useful in drug design and afford a unique advantage in the selection of analogous members.[23] Moreover, the lactim tautomers, even at lower concentrations, may induce errors in transcription and replication[24] in nucleic acid bases. Therefore their tautomerism is of relevance to the theory of spontaneous mutagenesis.[77]

It has been shown by a UV spectroscopic comparison with 1-methyl-2-pyrimidone 6 that 2-pyrimidinol 1 (2-pyrimidone), exists predominantly in the lactam 2 form in aqueous solution.[20] For 2- and 4-hydroxypyrimidines, a variety of physical methods[24,26,27] have shown that these compounds exist as cyclic amides in aqueous media. However, the reverse situation is found in the gas phase.[27] Some of the tautomeric constants are shown in Table I below. In the case of 4-pyrimidone protomer 4 predominates in the aqueous[20,28-30] and vapour phase. Beak remarked that at least one other protomer 3 or 5 was responsible for the weaker absorption in the gas phase.



1 ⇌ 2 I.1



3 ⇌ 4 + 5 I.2

Table I. Tautomeric Constants of 2- and 4-Pyrimidone.

Equilibrium	K_t (Vapour)[a,23]	K_t (Solution) Methanol[b,27]	H_2O[c,24,27]
1 ⇌ 2	< 0.1	> 15	2200
3 ⇌ 4 + 5	1.8 ± 1.0	> 4	340

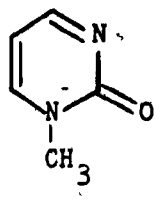
[a] Temperature of the vapour was 220°C.

[b] Ambient temperature.

[c] Obtained from pK_a data in aqueous solution.

Optimized MINDO/3 calculations[32] suggested that 5 is slightly more stable than 3 in the absence of solvent interaction. In general, the stabilization energy of the lactam form upon solvation is greater than that of the lactim form by about 5-8 Kcal/mol, as estimated from experimental data[27,33] and theoretical studies of the hydration effect.[34]

In this work N-methyl derivatives, for example 1-methyl-4-pyrimidone 7 and 3-methyl-4-pyrimidone 8, have been chosen to serve as models of their tautomeric counterparts 4-(1H)- and 4-(3H)-pyrimidone 4 and 5. This choice should ensure that any conclusion reached, in a mechanism or equilibrium, will be more reliable.[35]



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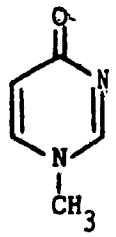

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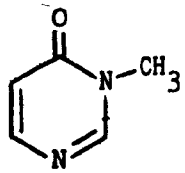

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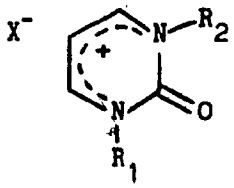

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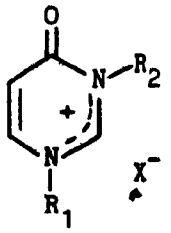


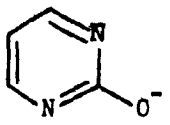
10

a $R_1 = R_2 = H$; b $R_1 = H$, $R_2 = CH_3$; c $R_1 = CH_3$, $R_2 = H$; d $R_1 = R_2 = CH_3$

Structures 9d and 10d were chosen to simulate the behaviour of the conjugate acid of 2 and 4, respectively, illustrated as 9a and 10a. These are written with a delocalized charge to indicate their major resonance forms.

More important, perhaps for the parent pyrimidones, is that they may undergo reaction via their anionic forms 11 and 12 at the physiological pH. These forms are comparable to phenoxide and

pyridoxide anions except for the two aza-nitrogens which can be treated as substituents (see later).



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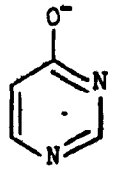


12

Because of tautomerism in the pyrimidine derivatives, the issue of nomenclature has always been plagued by confusion. For instance 4 can be named: 4-pyrimidone, 4-pyrimidinone, 4-pyridinol, 4-(1H)-pyrimidone, and 4-(3H)-pyrimidone. The last three names assume a specific tautomer as do 1,4-dihydro-4-oxo-pyrimidine and 3,4-dihydro-4-oxo-pyrimidine. The dihydro prefix has additional disadvantages of lengthening the name and wrongly implying a reduced state of the nucleus.[1] In this thesis the first name is adopted. Thus, 2 will be named 2-pyrimidone. But, when a specific structure or tautomer is to be named, the long form of the name is employed. Therefore, 9d will be named 1,4-(3,4)-dihydro-1,3-dimethyl-4-oxo-pyrimidinium... (X^-).

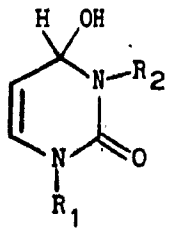
REACTIONS OF THE PYRIMIDONES

Covalent Adducts

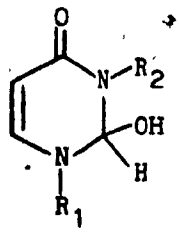
Nucleophilic addition across π-deficient aromatic and

heteroaromatic systems has been studied,[13,36-39] reviewed,[14-16] and continues to be researched. This meticulous attention stems in part from the relevance that covalent hydration has in biology. This, seems to lie in the direction of understanding the action of enzymes. For instance, xanthine oxidase catalyses the oxidation of aldehydes to acids, purines to hydroxypurines, and pteridines to hydroxypteridines with the common feature for these three substrates of a secondary alcoholic group present in the covalently hydrated forms.[14a]

Formal addition of water to an heterocycle gives rise to a covalent hydrate such as 13a-c, while a formal addition of hydroxide to a quaternary cation produces a pseudobase 13d.[14]



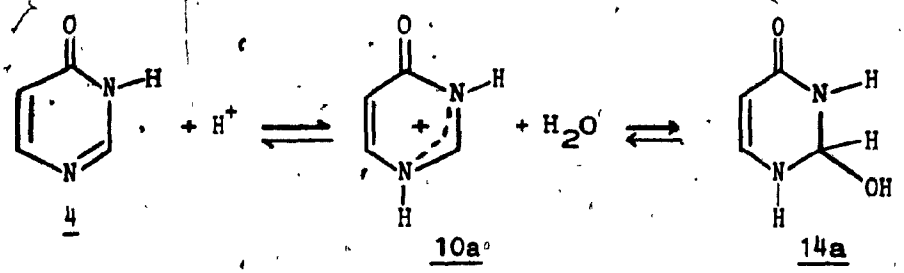
13



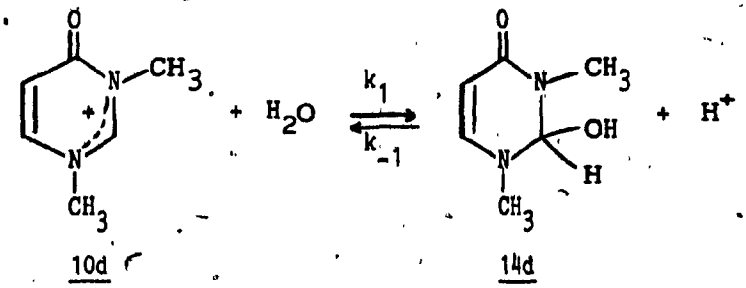
14

a $R_1 = R_2 = H$; b $R_1 = H$, $R_2 = CH_3$; c $R_1 = CH_3$, $R_2 = H$; d $R_1 = R_2 = CH_3$

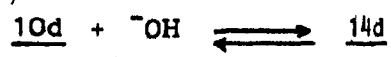
The processes 10a $\rightleftharpoons$ 14a and 10d $\rightleftharpoons$ 14d outlined in equations I.3 and I.4 are similar and thus, in acid medium, the distinction between covalent hydrate and pseudobase is not clear. Further complications arise when adducts with methanol, methoxide, ammonia, and amide are also termed covalent hydrates and pseudo-bases,[14,16] terms which were coined for water and hydroxide adducts respectively.



4 10a 14a I.3

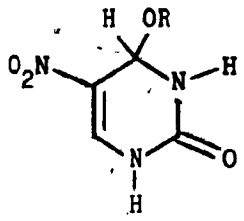


10d 14d I.4



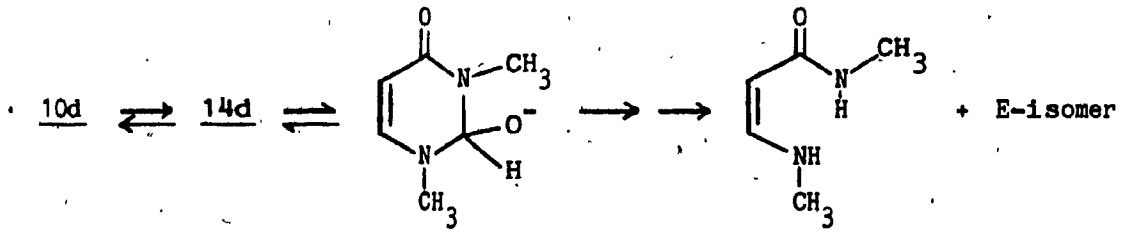
I.5

The nitro group in 5-nitro-2-pyrimidone stabilizes the covalent ethanol adduct 15 (R_1 = H, CH_2CH_3) permitting its isolation and identification.[38] However, the presence of the nitro group is not a necessity for their detection. Observation was possible for heterocycles containing one or two electron-withdrawing groups, where the presence of these hydrates caused deviations in some pK_as,[13] in electrophilic bromination,[17a,b,18,19] isotopic exchange,[39] and spectra.[13]



15

Moreover, the pseudobase 14d in base undergoes several distinct reactions with ring opening and ultimately formation of the amino acrylamide (10d → → → 16).[40]



16

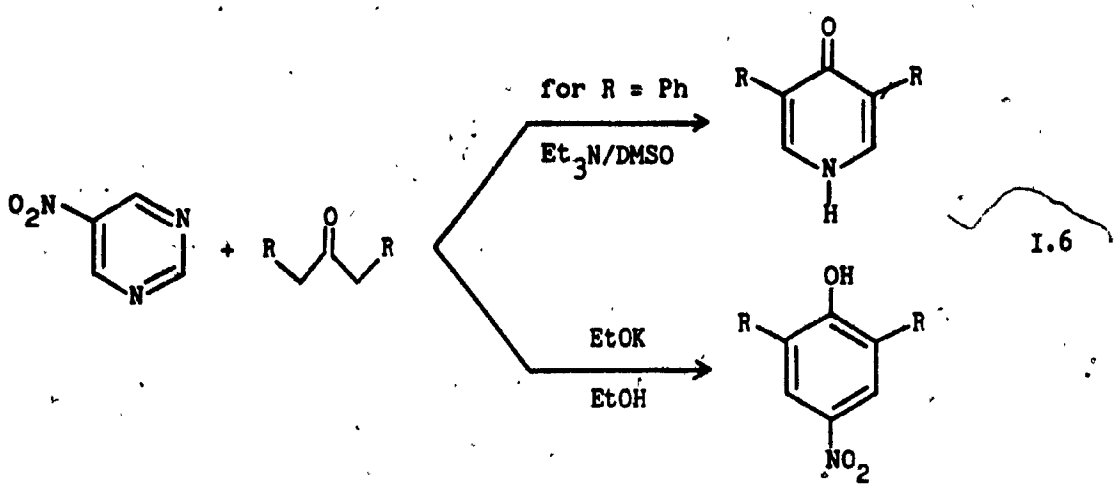
When the stronger nucleophile $^{-}NH_2$, in liquid ammonia, is reacted with 5-bromo-4-pyrimidone the 6-amino-4-pyrimidone is recovered.[41] This product presumably arises from the C-6 amino adduct formed because negative charge is induced, by initial ionization of the substrate, on the usual electropositive C-2 centre.[41]

On the other hand, ^{15}N-labelling experiments have shown that for 5-bromo-4-methoxypyrimidine (a model for a tautomer of 5-bromo-4-pyrimidone above without the labile hydrogen) when reacted with amide in liquid ammonia gives the usual C-2 amino adduct. This intermediate subsequently, through a ring-opening process, analogous to that found by Tee et al.,[40] produces the 6-amino-4-methoxypyrimidine.[41]

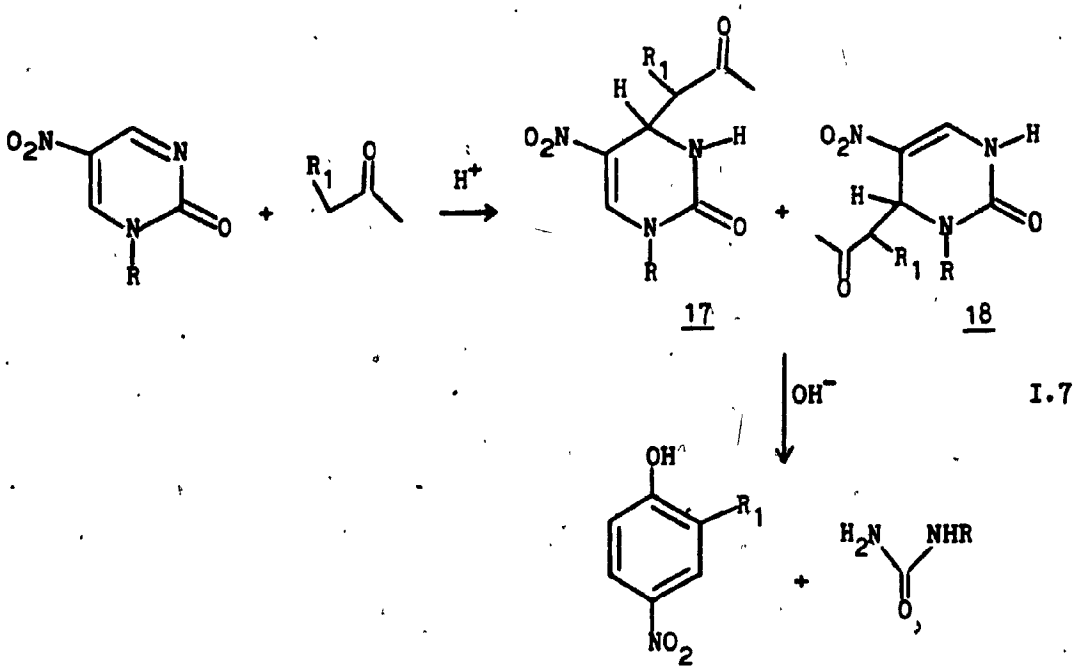
The importance of these adducts formed from amide and methoxide is their utility to serve as models for covalent hydrates and pseudobases, which otherwise would be unobservable. Such adducts have the property of not markedly altering the UV or NMR spectra vis-a-vis those resulting from attack of water. For instance, N-methyl pyridinium cation does not form a pseudobase in aqueous solution, but its properties could be conveniently studied in liquid ammonia. The amide ion is a much stronger nucleophile and the amino adduct forms readily for this substrate.[16]

Ring Transformations

The following newly-discovered ring transformations demonstrate a convenient path in the synthesis of some substituted pyridones[46] and phenols.[46,47] Van der Plas[46] has converted 1-methyl-pyrimidinium sulphate to 1,2-dihydro-2-oxo-nicotinic acid with ethyl acetoacetate. This reaction goes through formation of an adduct at C-6 (cf. covalent amination). Reaction of 5-nitro-pyrimidine[46] gave the products outlined in equation I.6. Fox[47] during studies aimed at synthesis of inhibitors of enzyme involved in pyrimidine metabolism, found a similar intermolecular transformation (cf. covalent hydration) outlined in equation I.7.



I.6



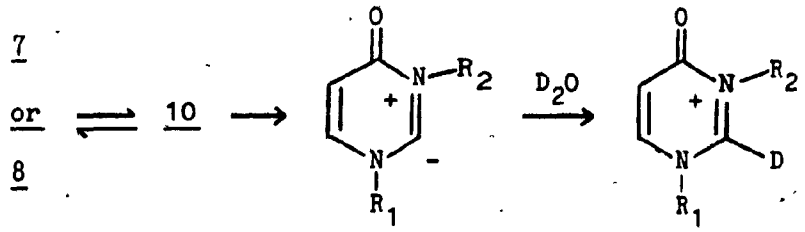
17 18

I.7

The ratio 17:18 for R = CH_3 was 9:2.[38] This may then be a good estimate, for the isomeric ratio of covalent hydrates 14c:14b, to be expected in aqueous solution.

Hydrogen-Deuterium Exchange

The most recent work on the H/D exchange of 4-pyrimidones was done by Beak.[42,43] This work proposed that the 4-pyrimidone series underwent a fast protonation equilibrium followed by rate-determining ylide formation and subsequent deuteriation at C-2, as shown in equation I.8.



I.8

Ylides have also been shown to be of importance in hydrogen-deuterium exchange of pyrimidine N-oxide.[44]

Katritzky et al. interpreted the increased reactivity of 10a-d versus the pyridones as occurring via their covalent hydrates 14a-c and pseudobases 14d.[39,45]

Disappointingly for Beak a comparison of 4-pyrimidinones with the pyridones was not possible. Hydrogen-deuterium exchange for these two sets of compounds proceeded via two different mechanisms as suggested by the base dependence on the N-methyl-2-pyridone and zero-order kinetics in base for 7 and 8.

Nitration

At the synthetic level[38] nitration of 2 occurs at C-5 in concentrated sulfuric acid/potassium nitrate medium with production of

15 (R = H), which is dehydrated, under vigorous conditions, to the 5-nitro-2-pyrimidone. 4-Pyrimidone is also nitrated, in the same medium, to give the 5-nitro-4-pyrimidone with no observable adducts.[38]

Kinetic studies[45] of the nitration of 2-pyrimidone and its N-methyl derivative, indicated that reaction at C-5 occurs via the depicted free-bases 2 and 6. This conclusion was confirmed by the unreactivity of the dimethyl cation 10d under comparable conditions. Katritzky[45] could not nitrate 4 as was reported.[38]

Bromination

The bromination of 2-pyrimidone and its derivatives 6, 9d, 21, 22d, and 24 (structures in Scheme I) was postulated to occur via covalent hydrates 13a-c, 23a-c, and pseudobases 13d and 23d.[18a,b,d] These substrates react rapidly with bromine to give observable intermediates which were converted to their respective 5-bromo or 5,5-dibromo products. The work of Banerjee[18a,b,d] afforded spectroscopic evidence of pseudobase 23d, the intermediates 19 and 25, and the ultimate products 21, 22d, and 24 (see Scheme I).

In strong acid solutions, kinetic evidence was obtained for the equilibrium 22 $\rightleftharpoons$ 23.[18d] A mechanistic study was subsequently carried out for the process 23 $\longrightarrow\longrightarrow$ 25.[18d]

The bromination of 9d could not be ascertained by Banerjee to proceed via the corresponding pseudobase 13d. However, from the inhibitory effect of acid upon 9d, where it exists > 99% as 9d, slow appearance of 22d, and by analogy with the methyl derivatives, he

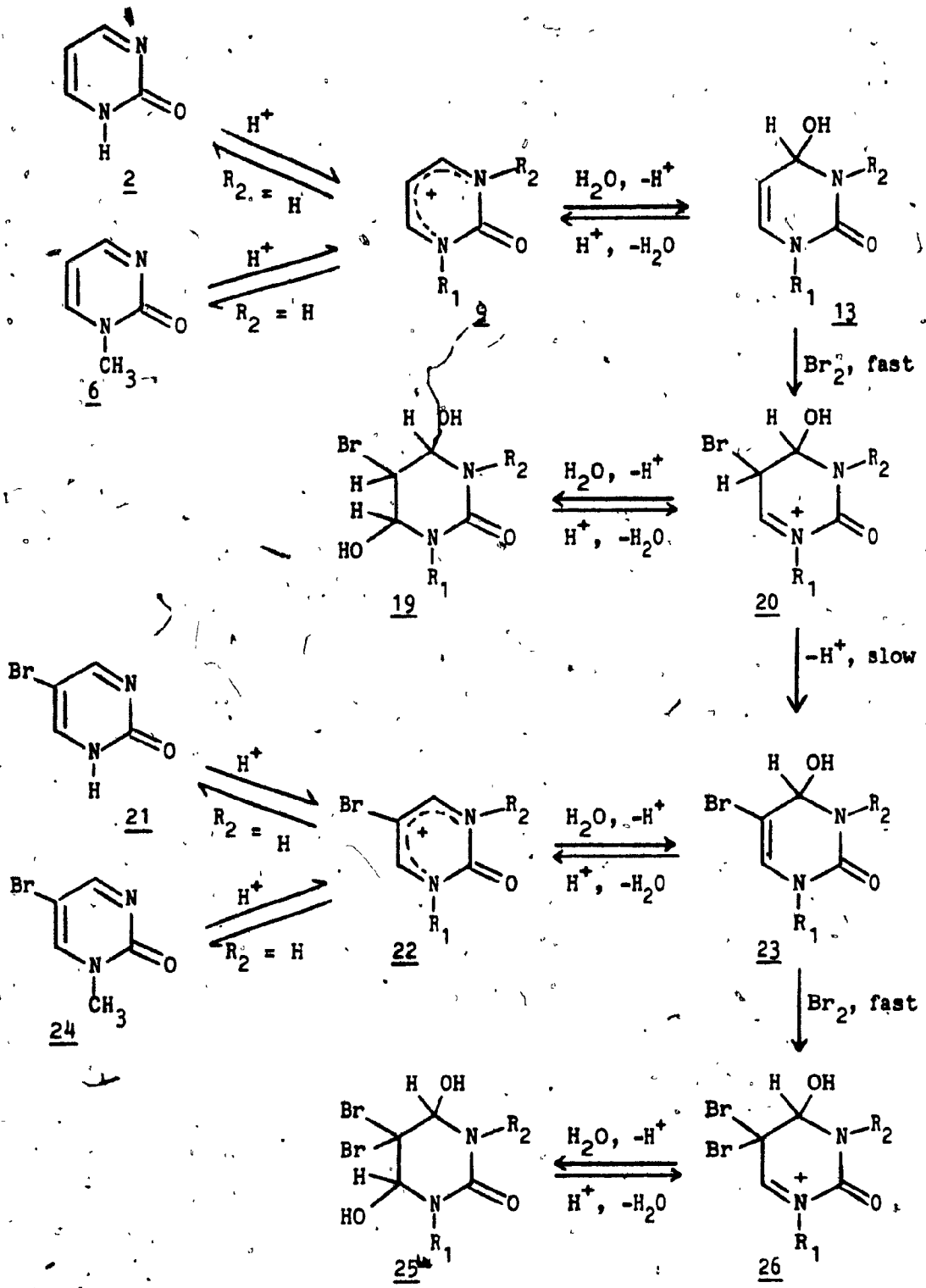
assumed that 13d was the reactive form. Stopped-flow kinetics on the bromination of 9d in weakly acidic solution and on its pseudobase formation and decomposition,[19] pointed convincingly to 13d as reacting with bromine (see Scheme I).

Thus, in Scheme I the processes 19 ⟶ ⟶ 25 had been studied and there was evidence for all but the intermediates 20 and 26. The only processes not studied were 2 and 6 ⟷ 9 ⟷ 13 ⟶ ⟶ 19. Kinetic evidence was needed for the covalent hydrates 13a-c.

This chapter will, inter alia, present data and discuss the bromination step 2 and 6 ⟶ ⟶ 19, which can be easily followed by stopped-flow UV spectroscopy. It also answers the query of Joule and Smith[48] as whether 2 itself is involved in the bromination step!

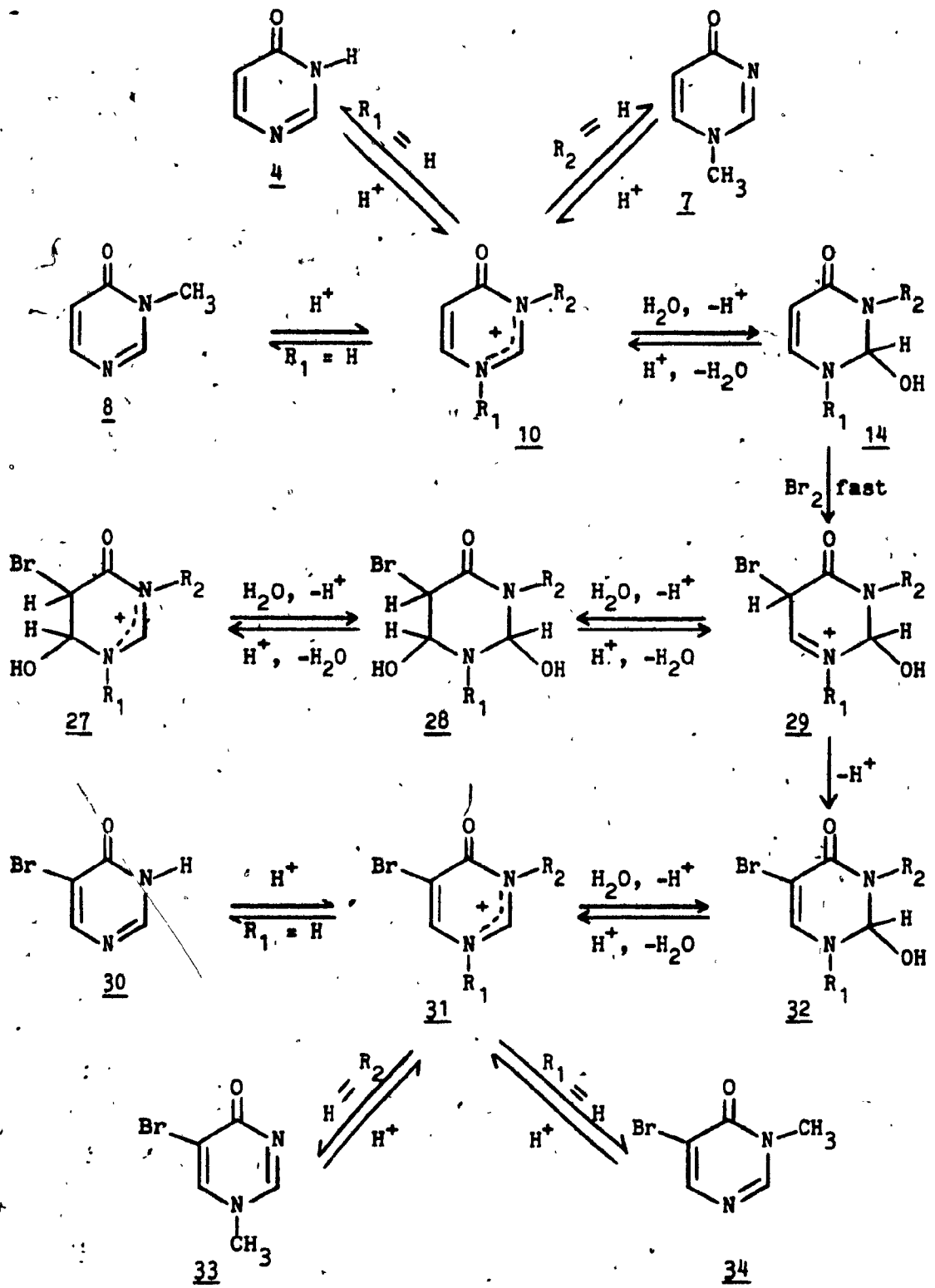
Electrophilic bromination of 4, 7, 8, and 10d were also studied by Banerjee[18c] at high acidity following the appearance of product 27 (Scheme II). However, he was unable to study the fast disappearance of bromine accompanying the reactions 14 ⟶ ⟶ 29. Similar spectroscopic evidence and deductions outlined as above for 2-pyrimidone and derivatives, suggested the intermediacy of covalent hydrates 14a-c and 32a-c and pseudobases 14d and 32d.[18c] (see Scheme II). The analysis of bromination products of the 5-bromo derivatives 31a-d were not pursued to the same extent mainly due to complexity leading to decomposition.[18c] Again by analogy with the steps 22 ⟶ ⟶ 25 (Scheme I), it was suggested that 31 initially produced 32 which brominated further (see equations I.68 and I.69).

Scheme I. Mechanism of Bromination of 2-Pyrimidones.[18b,d]



a $R_1 = R_2 = H$; b $R_1 = H$, $R_2 = CH_3$; c $R_1 = CH_3$, $R_2 = H$; d $R_1 = R_2 = CH_3$

Scheme II. Mechanism of Bromination of 4-Pyrimidones.[18c]



a $R_1 = R_2 = H$; **b** $R_1 = H$, $R_2 = CH_3$; **c** $R_1 = CH_3$, $R_2 = H$; **d** $R_1 = R_2 = CH_3$

RESULTS AND DISCUSSION

This chapter deals with the bromination of 2- and 4-pyrimidone and their N-methyl derivatives. This study was carried out by following the disappearance of bromine at the tribromide band ($_{max}$ = 266 nm). The pertinent UV data for the compounds with their pK_a values are summarized in Tables II and III.

For the parent substrates, the kinetics of bromination were carried out beyond pH 6 thereby uncovering four distinct pathways for consumption of the halogen. They are: (1) bromination of the covalent hydrate (or pseudobase), (2) the competitive bromination of the adducts, the free base, and the anion, (3) reaction of the free base, and (4) reaction of the anion of the parent substrate.

The earlier mechanistic proposal, that the initial bromination of 2-[18b,d] and 4-pyrimidone[18c] involves a covalent hydrate, can be generalized by the following equation I.9 and rate expression I.10.

$$P + H^+ \underset{K_{a1}}{\overset{\text{if R=H}}{\rightleftharpoons}} PR^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PROH + H^+ \xrightarrow{k_2,\ Br_2} \text{products} \qquad \text{I.9}$$

where $[PR^+]$ is the concentration of the conjugate acid 9 or 10 and [P] is the concentration of the free base of the substrate at a given time t. The rate of bromine disappearance is given by equation I.10.

$$\text{rate} = -d[Br_2]/dt = k_2[PROH][Br_2] \qquad \text{I.10}$$

Assuming a steady state concentration of PROH[19] then:

Table II. UV Spectral Parameters of the Pyrimidones.

Compound (Reference)	pK_a	pH or H_o	λ_{max} in nm (log ε)[a]
1,2-Dihydro-2-oxo-	2.24	0	309(3.75)
pyrimidine (20a)	9.17	6	298(3.68), 212(4.03)
		-[b]	292(3.66), 220(4.07)
1,2-Dihydro-1-methyl-2-oxo-	2.50	0.3	313(3.65)
pyrimidine (20a)		6	239(3.93), 296(2.70)
1,2-Dihydro-1,3-dimethyl-2-oxo-	7.03[c]	0.29	316(3.93), 215(>4.0)
pyrimidinium hydrogen	7.16[d]	10.1	239(3.93), 296(2.70)
sulphate (19,39c)			
3,4-Dihydro-4-oxo-	1.85[50]	-1.0	251(3.47), 224(3.69)
pyrimidine (30c,50)	8.60	6.2	260(3.57), 223(3.86)
	1.69[30c]	-[b]	263(3.55), 227(4.04)
1,4-Dihydro-3-methyl-4-oxo-	1.84	-0.4	258(3.47), 226(3.96)
pyrimidine (20d)		5	269(3.59), 221(3.83)
1,4-Dihydro-1-methyl-4-oxo-	2.02	0	250(3.42), 229(4.01)
pyrimidine (20d)		6	240(4.16)
1,4-Dihydro-1,3-dimethyl-4-	7.53[d]	2.0	266(3.46), 231(4.00)
oxo-pyrimidinium iodide[e]	7.54[d,f]	-[b]	289(3.96)[f]

[a] Underlined results are inflections or shoulders.

[b] [NaOH] = 0.10 M.

[c] Determined potentiometrically.

[d] This is pK_{R^+} at 30°C.

[e] This work.

[f] Obtained by extrapolation using the same approach as Fife.[51]

Table III. UV Spectral Parameters of the 5-Bromopyrimidones.

5-Bromo... (Reference)	pK_a	pH or H_o	λ_{max} in nm (log ϵ)
__-2-pyrimidone (52)	0.44	0.22	343(3.65), 222(4.19)
		4.0	322(3.54), 222(4.16)
__-1-methyl-2-pyrimidone (52)	0.55	-2.0	346(3.55), 224(3.96)
		4.0	326(3.43), 225(4.0)
__-1,2-dihydro-1,3-dimethyl-2-oxo-pyridinium bromide (18b)	3.08	0.29	346(3.85), 222(4.10)
		9.18	252(3.88), <200(>4.00)
__-4-pyrimidone (52)	0.43	-2.4	241(3.80), 273(3.73)
__-1-methyl-4-pyrimidone (18c)		0.29	246(3.91), 269(3.78)
__-3-methyl-4-pyrimidone (52)	0.14	-2.0	246(3.71), 277(3.78)
__-1,4-dihydro-1,3-dimethyl-4-oxo-pyrymidinium bromide (18c)		0.29	245(3.84), 277(3.72)

$$\text{rate} = \frac{k_1 k_2 [PR^+][Br_2]}{k_{-1}[H^+] + k_2[Br_2]} \qquad \text{I.11}$$

Since

$$[P]_o = [PR^+] + [P] + [Br_2]_o - [Br_2] \qquad \text{I.12}$$

where the subscript o refers to stoichiometric concentrations, then

$$[PR^+] = ([P]_o - [Br_2]_o + [Br_2])[H^+]/([H^+] + K_{a1}) \qquad \text{I.13}$$

For the dimethyl cations 9d and 10d, there exists no protonation equilibrium, thus:

$$[PR^+] = [PR^+]_o - [Br_2]_o + [Br_2] \qquad \text{I.14}$$

Reaction via tribromide has not been studied. This, however, should account for only 1-3% at most of the total reaction, when compared to the work of Bell[53] on anisoles and phenols. Its neglect, therefore, should not invalidate our mechanistic conclusions. However, a correction factor was incorporated in the determination of the second-order rate constant k_2, because the presence of bromide ions lowers the concentration of free bromine relative to its stoichiometric concentration. Bromine, in the presence of bromide ions, is partitioned in solution as outlined in equation I.15.

$$[Br_2]_T = [Br_2]_F + [Br_3^-] + [HOBr] + [BrO^-] \qquad \text{I.15}$$

In this equation $[Br_2]_T$ and $[Br_2]_F$ are the total and free (or reactive) concentrations of bromine at a given time respectively.

$$Br_3^- \overset{K_1}{\rightleftharpoons} Br_2 + Br^- \qquad \text{I.16}$$

$$Br_2 + H_2O \overset{K_2}{\rightleftharpoons} H^+ + Br^- + HOBr \qquad \text{I.17}$$

$$HOBr \underset{}{\overset{K_3}{\rightleftharpoons}} H^+ + {}^-OBr \qquad \text{I.18}$$

Thus,

$$K_1 = \frac{[Br_2][Br^-]}{[Br_3^-]} = 0.0554 \text{ M } (30^\circ\text{C and } 0.10 \text{ M I})^{54}$$

$$= 0.0625 \text{ M } (25^\circ\text{C and } 1.0 \text{ M I})^{55}$$

$$K_2 = \frac{[H^+][Br^-][HOBr]}{[Br_2]} = 9.6 \times 10^{-9} \text{ M}^2 \ (25^\circ\text{C})^{56}$$

$$K_3 = \frac{[{}^-OBr][H^+]}{[HOBr]} = 2.06 \times 10^{-9} \text{ M } (25^\circ\text{C})^{60b}$$

Assuming equilibrium conditions for all the species in equation I.15, the expression for $[Br_2]_T$ is:

$$[Br_2]_T = \left\{1 + \frac{[Br^-]}{K_1} + \frac{K_2}{([H^+][Br^-])} + \frac{K_2K_3}{([Br^-][H^+]^2)}\right\}[Br_2]_F \qquad \text{I.19}$$

Since

$$\text{rate} = -d[Br_2]_T/dt = k_2[Br_2]_F[PROH]$$

substituting $[Br_2]_F$ in equation I.19 into the rate expression obtains:

$$\frac{d[Br_2]_T}{dt} = \frac{k_2[Br_2]_T[PROH]}{\{1 + [Br^-]/K_1 + K_2/([H^+][Br^-]) + K_2K_3/([Br^-][H^+]^2)\}} \qquad \text{I.20}$$

It becomes obvious that the correction factor is given by the expression I.21:

$$\{1 + [Br^-]/K_1 + K_2/([H^+][Br^-]) + K_2K_3/([Br^-][H^+]^2)\} \qquad \text{I.21}$$

for a rate which is first-order with respect to bromine.

All substrates react readily with bromine in aqueous solution to

give the corresponding 5-bromo derivatives[18b,c] (see also Experimental section), although for synthetic purposes it was more convenient to use methanol as a solvent.

After complete disappearance of bromine there was a slow optical density increase assignable to the substitution products. For the purpose of analyzing the initial halogenation rate constant k_2, superficial product analysis was sufficient. Proton NMR results can be found elsewhere.[18b-d]

For an excess of substrate at fixed pH and high acidity, pseudo-first-order behaviour was observed. Equation I.11 explains the situation well, since for $k_{-1}[H^+] >> k_2[Br_2]$, its denominator reduces to $k_{-1}[H^+]$ and the rate expression is then given by equation I.22.

$$\text{rate} = (k_1k_2/k_{-1}[H^+])[PR^+][Br_2] \qquad \text{I.22}$$

At low acidities, when $k_2[Br_2] >> k_{-1}[H^+]$, pseudo-zero-order kinetics were observed. The rate expression I.11 reduces to equation I.23.

$$\text{rate} = k_1[PR^+] \qquad \text{I.23}$$

For this equation, the assumed inequality in equation I.11 will eventually break down as the reaction proceeds since $[Br_2]$ diminishes. Towards the end of the reaction, the traces again become first-order. However, analysis can still be performed in a conventional manner up to 90% reaction depending upon the acidity.

Where no such inequalities apply, the full expression for the rate must be employed. Substitution of I.13 into I.11 produces the integrable expression I.24.

$$\frac{-(d[Br_2])\{k_{-1}[H^+] + k_2[Br_2]\}}{([P]_o - [Br_2]_o)[Br_2] + [Br_2]^2} = \frac{[H^+]k_1k_2(dt)}{(K_{a1} + [H^+])} \qquad I.24$$

Therefore,

$$-\int_{[Br_2]_o}^{[Br_2]} \frac{k_{-1}[H^+](d[Br_2])}{([P]_o - [Br_2]_o)[Br_2] + [Br_2]^2} - \int_{[Br_2]_o}^{[Br_2]} \frac{k_2(d[Br_2])}{([P]_o - [Br_2]_o) + [Br_2]} =$$

$$[H^+]k_1k_2/(K_{a1} + [H^+])t \qquad I.25$$

This yields the following integrated equation I.26:

$$\frac{k_{-1}[H^+]}{k_2([P]_o - [Br_2]_o)} \ln \frac{[Br_2]_o([P]_o - [Br_2]_o + [Br_2])}{[P]_o[Br_2]} -$$

$$\ln \frac{([P]_o - [Br_2]_o + [Br_2])}{[P]_o} = \frac{[H^+]k_1t}{(K_{a1} + [H^+])} \qquad I.26$$

For the simple case where $[P]_o >> [Br_2]_o$, I.24 can be rewritten as:

$$\frac{-(d[Br_2])(k_{-1}[H^+] + k_2[Br_2])}{([P]_o[Br_2])} = \frac{[H^+]k_1k_2\ (dt)}{(K_{a1} + [H^+])} \qquad I.27$$

which integrates into:

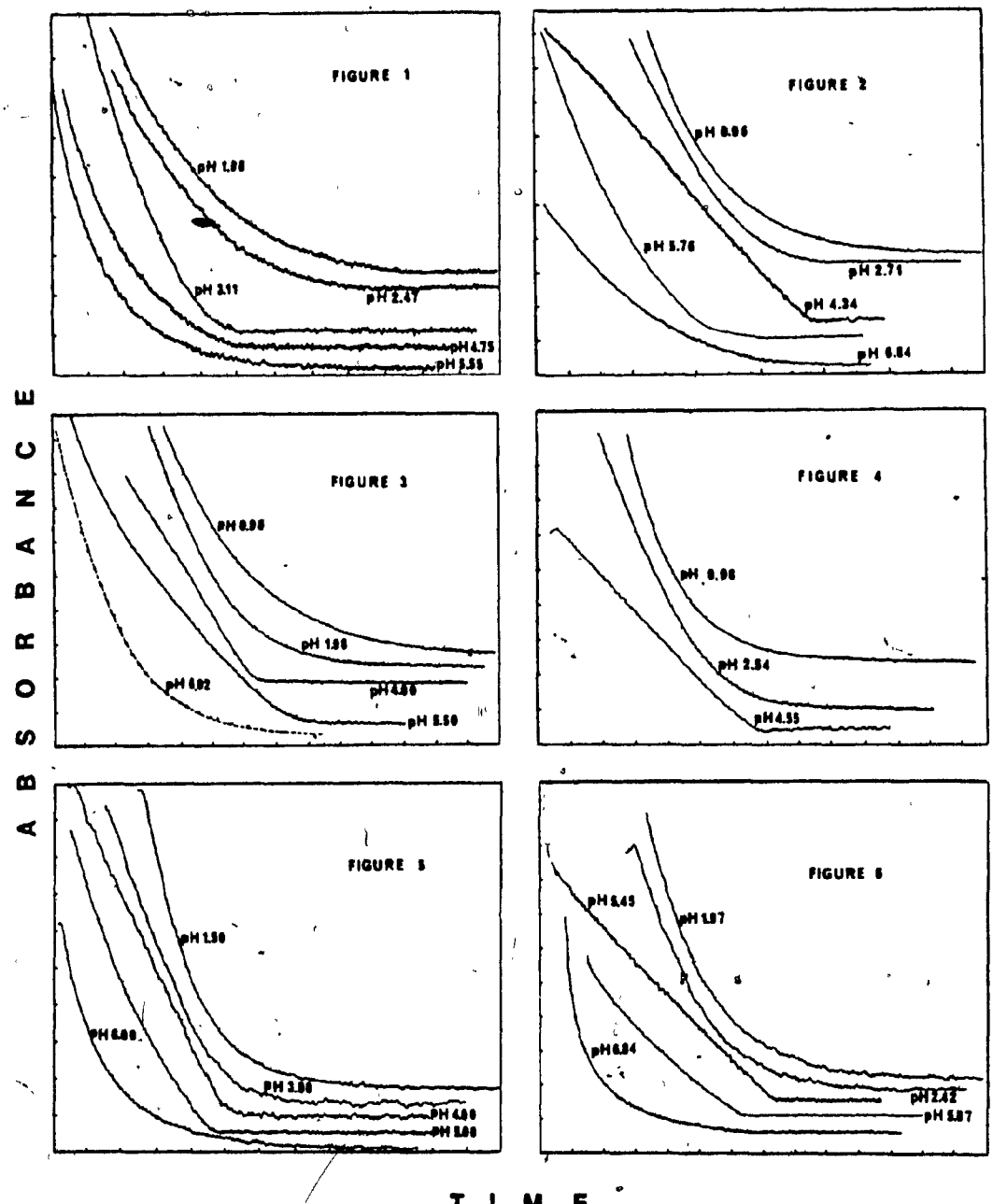
$$\frac{k_{-1}[H^+]}{k_2}\left\{\ln \frac{[Br_2]_o}{[Br_2]}\right\} + ([Br_2]_o - [Br_2]) = \frac{[H^+]k_1[P]_ot}{(K_{a1} + [H^+])} \qquad I.28$$

On the other hand, subtitution of I.14 into I.11, and applying the same logic and assumptions as above, the simplest expression I.29 for the quaternary cation can be derived:

$$\frac{k_{-1}[H^+]}{k_2} \ln\left\{\frac{[Br_2]_o}{[Br_2]}\right\} + ([Br_2]_o - [Br_2]) = [PR^+]_o k_1 t \qquad \text{I.29}$$

This last equation, and similarly I.28, can be analyzed as shown in Experimental (page 218).

Altogether, the observations consistent with equations I.22, I.23, I.28, and I.29 were realized for all of the substrates studied. Samples of experimental traces for each compound are reported in Figures 1-6.



Figures 1-6. Sample traces of absorbance versus time from bromination of 4-pyrimidone, 1-methyl-4-pyrimidone, 3-methyl-4-pyrimidone, 1,3-dimethyl-4-oxo-pyrimidinium perchlorate, 2-pyrimidone, and 1-methyl-2-pyrimidone at different pHs respectively. Note the changes in order for increasing pH: first, mixed, zero, mixed, and first.

4-PYRIMIDONE AND ITS DERIVATIVES

The bromination data for this series of compounds are reported in Tables IV-VI and IX. For the purpose of clear analysis, the results are divided into pH regions.

pH 0-1.22

The kinetic order in this medium is pseudo-first. The increase in k_2^{obsd} with decreasing acidity, as shown in Figure 7 (dotted lines), excludes the conjugate acid forms 10a-c as the reacting species by contrast to 10d which also shows similar profile. This quaternary salt, if it were reacting as 10d, should have produced a zero-slope rate profile in this region. Reactivities on the free bases 4, 7, and 8 were also excluded on the basis of the observed kinetic behaviour beyond their respective pK_{a1}s (see later).

A constant positive salt effect is illustrated in Figure 7. The magnitude of this effect is 1.5. Superimposed on this is some other effect or reactive intermediate causing curvature in the rate profiles for the most acidic region studied. The slopes taken from the two runs at pH -0.035 and 0.264 are calculated from Table IV to be 0.55, 0.53, 0.47, and 0.62 for 4, 7, 8, and 10d respectively. The overall trend for the rate profiles is towards a zero slope. This result may point to another intermediate brominating competitively with the covalent hydrate (pseudobase) and/or possibly changes in ionic strength of the buffer alters the activity coefficients and the pH as a consequence.

Table IV. Second-order Rate Constants for the Reaction of Bromine with 4-Pyrimidones at High Acidity and High Ionic Strength (I = 1.1).[a]

Derivative of 4-Pyrimidone (Structure Number)	pH	$[P]_o$ or $[PR^+]_o$ X 10^5 M	k_1^{obsd} X 10^3 sec^{-1}	k_2^{obsd} X 10^{-2} M^{-1} sec^{-1}
___ (4)	-0.035[b,c]	200	12.1	1.30
	0.264[b,d]	200	17.1	1.90
	0.614[b,e]	200	30.4	3.22
	0.908[b,f]	200	49.1	5.24
	1.22[g]	200	83.4	8.89
1-Methyl-___ (7)	-0.035[b,c]	200	30.1	3.21
	0.264[b,d]	200	41.6	4.61
	0.614[b,e]	200	77.9	8.23
	0.908[b,f]	200	140	14.9
	1.22[g]	200	249	26.6
3-Methyl-___ (8)	-0.035[b,c]	200	5.29	0.566
	0.264[b,d]	200	7.05	0.783
	0.164[b,e]	200	13.4	1.43
	0.908[b,f]	200	23.6	2.52
	1.22[g]	200	41.6	4.44
1,3-Dimethyl-___ (10d, X = ClO_4^-)	-0.035[b,c]	200	23.9	2.55
	0.264[b,d]	200	35.2	3.92
	0.614[b,e]	200	61.7	6.52
	0.908[b,f]	200	111	11.9
	1.22[g]	200	206	22.0

[a] At 30°C, $[Br_2]_o$ = 5.0 X 10^{-5} M. Each datum is the average of at least three runs. Correlation coefficients are > 0.9995.

[b] pH = -log[HBr].

[c] ([HBr] + [KBr]) = 1.100 M, [d] 1.144 M, [e] 1.088 M, [f] 1.098 M, [g] 1.097 M.

Table V. Second-order Rate Constants for the Bromination of 4-Pyrimidones at High Acidity.[a]

4-Pyrimidone Derivative	pH	$[P]_o$ or $[PR^+]_o$ X 10^6 M	k_1^{obsd} sec^{-1}	k_2^{obsd} X 10^{-3} M^{-1} sec^{-1}
___ (4)	0.96	200		0.468[b]
		400		0.455[b]
		750		0.463[b]
		1000		0.453[b]
	1.26	500	0.0868	0.541
		750	0.123	0.493
	1.56[c]	2000	0.648	0.993[d]
	1.78	2000	0.858	1.31[e]
		4000	1.92	1.46[e]
	1.98	2000	0.973	1.40
	2.06[c]	2000	1.07	1.55
	2.34[c]	1500	1.02	1.98
	2.64[c]	2000	1.50	2.16
	2.95[c]	1500	1.28	2.47
		2000	1.62	2.33
1-Methyl ___ (7)	0.96	500	0.195	1.29
		750	0.278	1.18
		1000	0.378	1.19
		1500	0.583	1.20
		2000	0.780	1.19
	1.48	1000	0.818	2.57[f]
		2000	1.62	2.48[f]

Table V. Continued.

4-Pyrimidone Derivative	pH	$[P]_o$ or $[PR^+]_o$ X 10^6 M	k_1^{obsd} sec^{-1}	k_2^{obsd} X 10^{-3} M^{-1} sec^{-1}
1-Methyl ___ (7)	1.98[c]	1000	1.77	5.23
		2000	3.60	5.18
	2.71[c]	500	1.56	9.72
		1000	3.43	10.1
	3.36[c]	500	2.11	13.2
		1000	3.72	11.0
3-Methyl ___ (8)	0.96	500		0.184[b]
		625		0.178[b]
		750		0.177[b]
		1000		0.180[b]
		1500		0.181[b]
		2000		0.179[b]
	1.48	1000	0.144	0.452[f]
		2000	0.294	0.450[f]
	1.98[c]	1000	0.291	0.859
		2000	0.532	0.765
	2.71[c]	500	0.233	1.45
		1000	0.491	1.45
1,3-Dimethyl ___ (10d X = ClO_4)	0.96	500	0.168	1.11
		1000	0.402	1.26
	1.26	500	0.298	1.86
		1000	0.732	2.16

Table V. Continued.

4-Pyrimidone Derivative	pH	$[P]_o$ or $[PR^+]_o$ X 10^6 M	k_1^{obsd} sec^{-1}	k_2^{obsd} X 10^{-3} M^{-1} sec^{-1}
1,3-Dimethyl ___	1.78	200		5.19[b,e]
(10d X = ClO_4^-)		400		5.30[b,e]
	2.05	200		8.56[b]
		300		8.47[b]
		400		8.81[b]
	2.42[c]	200	1.29	24.2
		400	2.83	22.7
	2.53[c]	250	2.32	32.5
		500	5.35	33.3
		1000	10.9	32.2
	2.95[c]	500	13.6	85.0
		1000	27.8	81.9

[a] At 30°C, $[Br_2]_o$ = 5 X 10^{-5} M, $[Br^-]_T$ = [HBr] + [KBr] = 0.100 M, I = 0.110 M except where otherwise noted. Correlation coefficients are better than 0.9995 except for mixed-order kinetics where they are better than 0.999.

[b] Obtained directly from second-order analysis and corrected for tribromide ion formation.

[c] From mixed-order analysis.

[d] $[Br^-]_T$ = 0.1075 M, [e] 0.1088 M, [f] 0.1111 M.

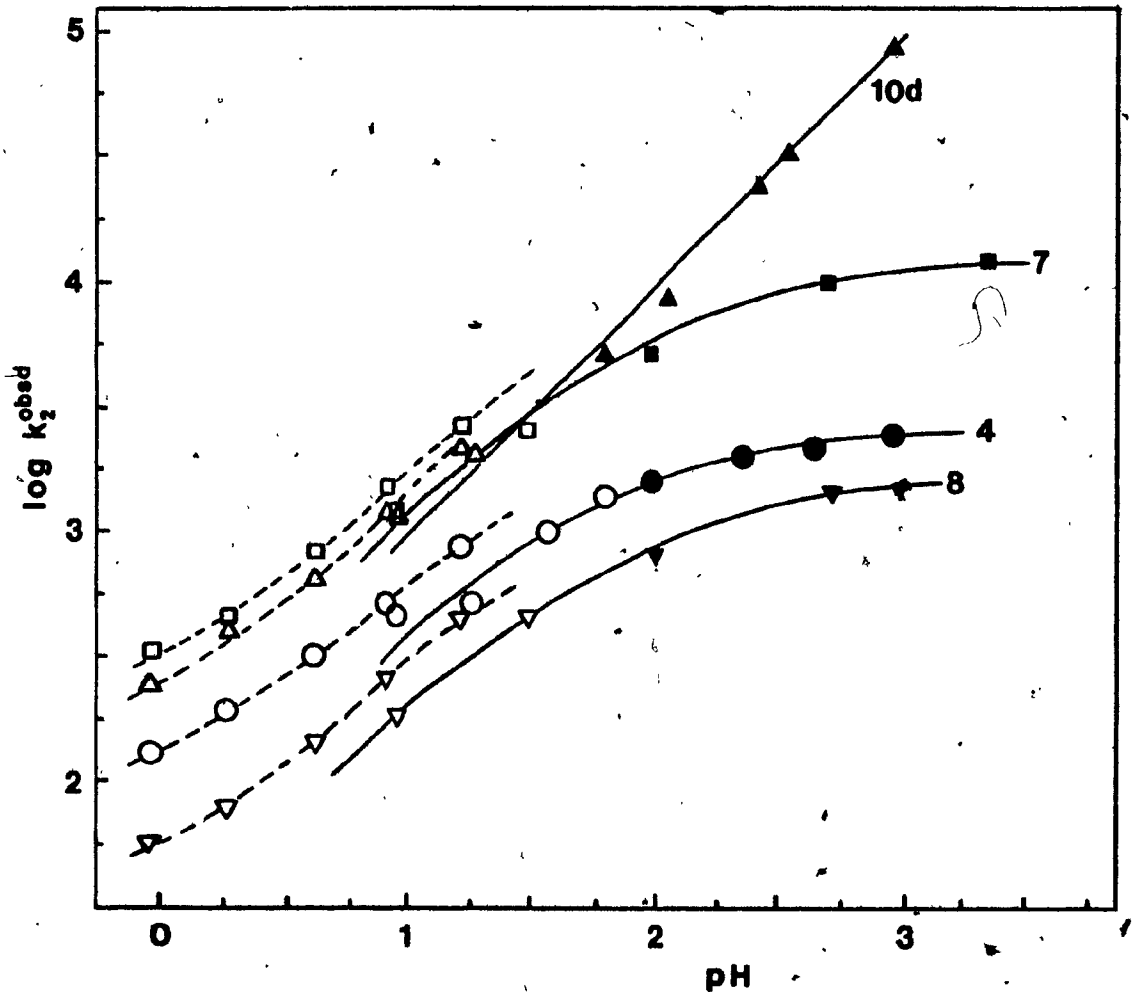


Figure 7. pH rate profiles for the reaction of bromine with 4-pyrimidone 4 (○, ●), 1-methyl-4-pyrimidone 7 (□, ■), 3-methyl-4-pyrimidone 8 (▽, ▼), and 1,3-dimethyl-4-oxo-pyrimidinium perchlorate 10d (△, ▲). The average ionic strength is 1.1 M (dashed lines) and 0.11 M (solid lines) respectively.

pH 1.22-2

At a given pH in the presence of excess substrate, measuring bromine disappearance afforded pseudo-first-order rate constants

(k_1^{obsd}) which varied linearly with substrate concentration (see Table V and Figure 7 solid lines). Some kinetic runs, which were carried out for substrate concentrations not in large excess, were analyzed directly for second-order behaviour employing equation I.22 in conjunction with I.13 or I.14. Thus, for 10a-c the first-order and second-order rate constants are given by equations I.30 and I.31 respectively.

$$k_1^{obsd} = k_1k_2([P]_o - [Br_2]_o)/\{k_{-1}(K_{a1} + [H^+])\} \qquad I.30$$

$$k_2^{obsd} = k_1k_2/\{k_{-1}([H^+] + K_{a1})\} \qquad I.31$$

For substrate 10d integration of equation I.22, after substitution of I.14, gave simpler forms for the observed rate constants illustrated in I.32 and I.33.

$$k_1^{obsd} = k_1k_2([PR^+]_o - [Br_2]_o)/\{k_{-1}[H^+]\} \qquad I.32$$

$$k_2^{obsd} = k_1k_2/\{k_{-1}[H^+]\} \qquad I.33$$

Values of k_2^{obsd} obtained from straight second-order analysis are denoted by superscript e in Table V.

Altogether, the data in this region are consistent with equation I.22 and are plotted with open symbols in Figure 7. In this figure, the straight line of unit slope for 10d was drawn assuming that $k_2k_1/k_{-1} = k_2K_{R^+} = 97.5\ sec^{-1}$. Since $pK_{R^+} = 7.53$ (Table II), $K_{R^+} = 2.95 \times 10^{-8}$ M, and so $k_2 = 3.3 \times 10^9\ M^{-1}\ sec^{-1}$.

For the other substrates, similar behaviour was observed, with a tendency for the rate profile to level off as the pH values approached their protonation pK_{a1}s. Since in this region the substrate is largely protonated as 10a-c, the pH dependence of k_2^{obsd} obeyed equation I.31

where $K_{a1} << [H^+]$. The curves were plotted using a curve-fitting program through the experimental points and assuming only one value for K_{a1} or K_R+ for Figure 7 and Figure 8.

pH 2-3

In this region mixed-order kinetics were observed. This order can be distinguished from a simple exponential decay (see Figures 1-6) by two distinct features. The beginning portion of the absorbance trace forms a straight line. Second, towards the end of the reaction, the curvature, for mixed-order kinetics, is greater than for simple exponential.

The analysis described in the experimental section was similar to that of Challis and Rzepa.[57] The first-order component k_1^{obsd} was extracted from the data by treatment with equation I.28 (I.29 for 10d), where k_1^{obsd} and k_2^{obsd} were those given in equation I.30 and I.31 (I.32 and I.33 for 10d) respectively. Values of these rate constants are given in Table V and denoted by superscript f. Values of k_2^{obsd} were plotted as closed symbols in Figure 7 and behaved as expected from equation I.31 or I.33.

The zero-order component was also extracted from equation I.23 for 4, 7, and 8 as:

$$k_o^{obsd} = [P]_o[H^+]k_1/(K_{a1} + [H^+]) \qquad \text{I.34}$$

While for 10d k_o^{obsd} is given by I.35.

$$k_o^{obsd} = [PR^+]_o\, k_1 \qquad \text{I.35}$$

From these pseudo-zero-order rate constants are derived the

$k_1^{obsd'}$ by dividing by $[P]_o$ for 4, 7, and 8 and $[PR^+]_o$ for 10d. These are represented by I.36 and I.37.

$$k_1^{obsd'} = [H^+]k_1/(K_{a1} + [H^+]) \qquad \text{I.36}$$

$$k_1^{obsd''} = k_1 \qquad \text{I.37}$$

Values of zero-order rate constants obtained from mixed-order analysis are denoted with superscript b in Table VI and plotted as closed symbols in Figure 8.

pH 3-5

In this region the disappearance of bromine in the presence of an excess of substrate exhibited pseudo-zero-order behaviour (see Figures 1-6), and k_o^{obsd} varied linearly with substrate concentrations as expressed in equations I.34 and I.35. Values of k_o^{obsd} and $k_1^{obsd'}$ are presented in Table VI and depicted as open symbols in Figure 8.

For the substrates 4, 7, and 8, where $K_{a1} >> [H^+]$, $k_1^{obsd'}$ decreases with increasing pH, thus verifying equation I.36. However, for 10d, $k_1^{obsd'}$ should be independent of acidity of the medium (eq I.37). Again, this is what is seen in Figure 8 and the value of k_1 was corroborated by an equilibration study (see later). The rate constant k_1 corresponds to attack of water upon 10d, leading to the pseudobase 14d, with a magnitude of 0.26 sec^{-1}. for this compound, since $K_{R^+} = 2.95 \times 10^{-8}$ M (Table III), k_{-1} is then calculated from equation I.33 to be 8.8×10^6 $M^{-1}sec^{-1}$.

Table VI. First-order Rate Constants for the Bromination of 4-Pyrimidones at Low Acidity.[a]

4-Pyrimidone Derivative	pH	$[P]_o$ or $[PR^+]_o$ X 10^6 M	k_o^{obsd} X 10^5 M sec^{-1}	k_1^{obsd} X 10^2 sec^{-1}
___ (4)	2.06[b]	2000	16.1	8.05
	2.34[b]	1500	8.10	5.40
		2000	10.4	5.18
	2.64[b]	2000	6.02	3.01
	2.95[b]	1500	2.43	1.62
		2000	3.26	1.63
	3.11	2000	1.94	0.972
	3.36	1500	0.991	0.661
	3.55	1500	0.796	0.531
		2000	1.03	0.513
	3.72[c]	2000		0.260
		2500		0.246
	4.25[c]	2000		0.0946
		2500		0.0869
1-Methyl ___ (7)	1.98[b]	1000	12.0	12.0
		2000	24.0	12.0
	2.71[b]	500	2.96	5.91
		1000	4.17	4.17
	3.36[b]	500	0.610	1.22
		1000	1.39	1.39
	3.70	1000	0.561	0.561
	4.00	1000	0.328	0.328
	4.40	1000	0.185	0.185
		2000	0.412	0.206
	5.05[c]	2000		0.0378
	5.50[c]	1500		0.0117

Table VI. Continued.

4-Pyrimidone Derivative	pH	$[P]_o$ or $[PR^+]_o$ X 10^6 M	k_o^{obsd} X 10^5 M sec^{-1}	$k_1^{obsd'}$ X 10^2 sec^{-1}
3-Methyl ___ (8)	1.98[b]	1000	3.45	3.45
		2000	7.80	3.90
	2.71[b]	500	0.595	1.19
		1000	1.13	1.13
	3.36	500	0.130	0.260
		1000	0.270	0.270
	3.69	1000	0.188	0.188
	3.99	1000	0.168	0.168
	4.34	1000	0.0650	0.0650
		2000	0.140	0.0700
	4.97	2000	0.0449	0.0225
	5.09[c]	2000		0.0146
	5.53[c]	2000		0.00616
	5.76[c]	2000		0.00310
1,3-Dimethyl-___ (10d X = ClO_4^-)	2.42[b]	200	5.64	28.2
		400	10.8	26.9
	2.53[b]	250	6.12	24.5
		500	12.0	24.0
		1000	25.2	25.2
	2.95[b]	500	12.2	24.5
		1000	24.9	24.9
	3.32	250	5.06	20.2
		500	10.3	20.5
	3.96	500	15.0	30.0
		1000	30.2	30.2
	4.23	300	8.52	28.4
	4.55	100	2.68	26.7

[a] Same as footnote a in Table V.

[b] From mixed-order analysis equations I.28 and I.29. See text pages 27 and 28.

[c] From different mixed-order analysis equation I.52. See text section: pH 4-7.

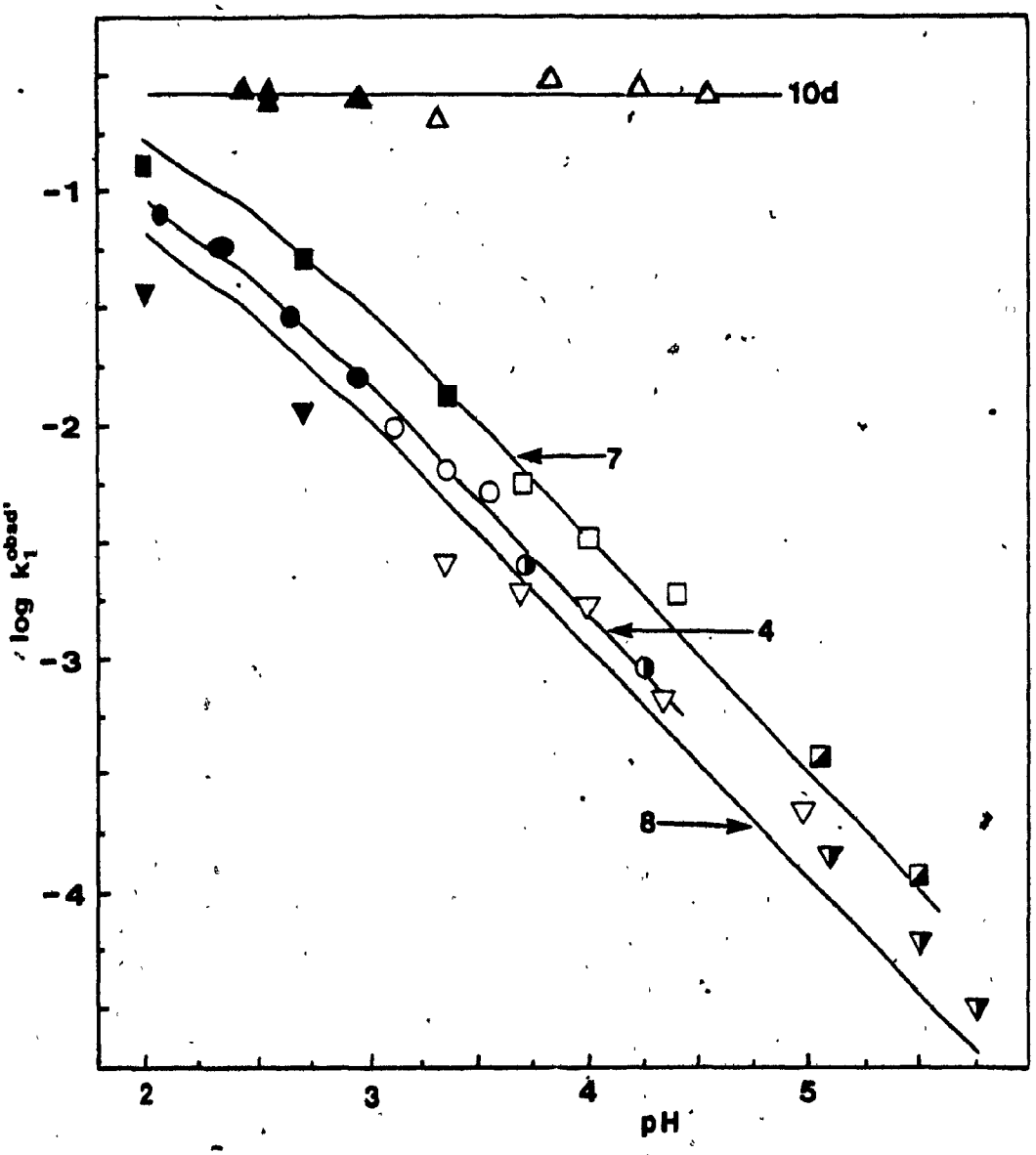


Figure 8. Plots of $k_1^{obsd'}$ versus pH for 4-pyrimidone 4 (●, ○, ◑), 1-methyl-4-pyrimidone 7 (■, □, ◪), 3-methyl-4-pyrimidone 8 (▼, ▽, ▽), and 1,3-dimethyl-4-oxo-pyrimidinium perchlorate 10d (▲, △) illustrating the changeover in rate orders: mixed from first (shaded symbols), zero (open symbols), and mixed from zero (partially shaded symbols). The fitted k_1 (eq I.9) are 0.24 ± 0.02, 0.32 ± 0.03, 0.15 ± 0.10, and 0.26 ± 0.03 sec^{-1} respectively.

The above rate constants also support the use of the steady state assumption in deriving equation 11. Up to pH 2 a pseudo-first-order process arose from the inequality $k_{-1}[H^+] >> k_2[Br_2]$, where k_2 for 10d was calculated to be 3.3×10^9 $M^{-1}sec^{-1}$. Therefore,

$$\min(k_{-1}[H^+]) = (8.8 \times 10^6)(1 \times 10^{-2}) = 8.8 \times 10^4 \text{ sec}^{-1}$$

$$\max(k_2[Br_2]) = (3.3 \times 10^9)(5 \times 10^{-5}) = 1.6 \times 10^5 \text{ sec}^{-1} \quad (t = 0)$$

and only after mixing at pH 2 were these two terms comparable. But, as the reaction proceeded, (i.e. $[Br_2] \longrightarrow 5 \times 10^{-6}$ M for 90% reaction) $k_{-1}[H^+] >> k_2[Br_2]$ is a true inequality. For pH < 2, it can be shown that the inequality holds for all times.

At pH 3 and above, the assumption was that $k_{-1}[H^+] << k_2[Br_2]_o$:

$$\max(k_{-1}[H^+]) = (8.8 \times 10^6)(1 \times 10^{-3}) = 8.8 \times 10^3 \text{ sec}^{-1}$$

$$\min(k_2[Br_2]) = (3.3 \times 10^9)(5 \times 10^{-6}) = 1.6 \times 10^4 \text{ sec}^{-1} \quad \text{(90\% reaction completion)}$$

Thus, the inequality holds true for pH > 3.

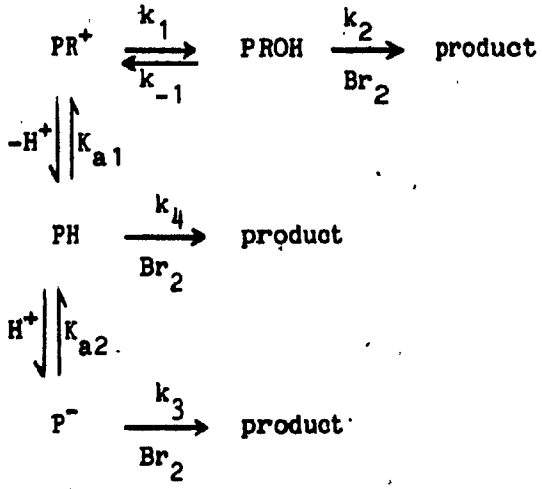
The acidity dependence shown by k_1^{obsd} values for 4, 7, and 8 in Figure 8 are explicable by rate-determining attack of water upon the conjugate acids 10a-c, forming the covalent hydrates 14a-c. A feature of the data plotted in this figure was the presence of deviations above the calculated curves mostly evident for the 3-methyl derivative 8. These deviations were ascribed to incursion of succinate buffer catalysis, particularly since the dimethyl cation 10d showed buffer catalysis (see later).

In summary, the data for all the four substrates over a wide range $0 < pH < 5$ is explicable by the mechanism of equation I.9 and its rate law equation I.11. Bromination occurs on 14 from the cation 10 with the rate-determining step depending upon the acidity. But in the next section the mechanism is more complex, though simple analysis was sufficient to place all information in the proper perspective.

The Competitive Mechanism

In Figures 1-4 different kinetic behaviour can be seen in the region $4 < pH < 7$. This is due to a second type of mixed-order kinetics which can be deduced for the anion of the parent 4, the free base, and the covalent hydrate reacting competitively according to Scheme III.

Scheme III. Competitive Bromination of the 2- and 4-Pyrimidones.



The rate law for this scheme is:

$$-d[Br_2]/dt = k_3[Br_2][P^-] + k_4[Br_2][P] + k_2[Br_2][PROH] \qquad I.38$$

Substituting for all the equilibria in terms of [P] the rate law is:

$$\text{rate} = \left\{[Br_2] + \frac{k_1k_2[H^+][Br_2]}{K_{a1}\left\{\frac{k_3K_{a2}}{[H^+]} + k_4\right\}(k_{-1}[H^+] + k_2[Br_2])}\right\}\left\{\frac{k_3K_{a2}}{[H^+]} + k_4\right\}[P] \qquad I.39$$

Where from equation I.12 and I.13 the expression for [P] is:

$$[P] = \frac{[P]_o - [Br_2]_o + [Br_2]}{1 + K_{a2}/[H^+] + [H^+]/K_{a1}} \qquad I.40$$

Let

$$A = \frac{k_1k_2[H^+][Br_2]}{K_{a1}(k_3K_{a2}/[H^+] + k_4)(k_{-1}[H^+] + k_2[Br_2])} \qquad I.41$$

and

$$B = \frac{(k_3K_{a2}/[H^+] + k_4)}{(1 + K_{a2}/[H^+] + [H^+]/K_{a1})} \qquad I.42$$

then,

$$\text{rate} = ([Br_2] + A)B([P]_o - [Br_2]_o + [Br_2]) \qquad I.43$$

For $k_{-1}[H^+] \ll k_2[Br_2]$, where this inequality must be true in this pH range (see above), A is a constant value given by:

$$A = \frac{k_1[H^+]}{K_{a1}(k_3K_{a2}/[H^+] + k_4)} \qquad I.44$$

The rate expression can be rewritten in the integral form:

$$\int_{[Br_2]_o}^{[Br_2]} \frac{d[Br_2]}{([Br_2] + A)\{([P]_o - [Br_2]_o) + [Br_2]\}} = -Bt \qquad I.45$$

Let $q = 4A([P]_o - [Br_2]_o) - \{([P]_o - [Br_2]_o) + A\}^2$

$= - \{([P]_o - [Br_2]_o) - A\}^2$

Thus, for $q < 0$ (i.e. $[P]_o > [Br_2]_o + A$), this expression can be integrated[60a] into:

$$\ln \frac{[Br_2] + A}{[Br_2] + ([P]_o - [Br_2]_o)} \Bigg|_{[Br_2]_o}^{[Br_2]} = -([P]_o - [Br_2]_o - A)Bt \qquad I.46$$

or

$$\frac{([Br_2] + A)}{([Br_2]_o + A)([Br_2] + [P]_o - [Br_2]_o)} = \frac{\exp\{(A + [Br_2]_o - [P]_o)Bt\}}{[P]_o} \qquad I.47$$

Therefore

$$[Br_2] = \frac{\left\{\frac{([P]_o - [Br_2]_o)([Br_2]_o + A)}{[P]_o} \exp\{([Br_2]_o - [P]_o + A)Bt\}\right\} - A}{1 - \frac{([Br_2]_o + A)}{[P]_o} \exp\{([Br_2]_o - [P]_o + A)Bt\}} \qquad I.48$$

The value of B has no boundary in this equation. Suppose that $B = 10\ M^{-1}sec^{-1}$ $[P]_o = 2 \times 10^{-3}$ M, and $[Br_2]_o = .5 \times 10^{-5}$ M. If A is varied from 10^{-4} M to a small value say 10^{-7} M, then the evaluation of $[Br_2]$ as a function of time is possible from equation I.48. These

values are represented in Table VII and plotted in Figure 9.

Table VII. Values of $[Br_2]$ Obtained from Equation I.47 at Different Values of A Assuming B = 10 $M^{-1}sec^{-1}$, $[P]_o$ = 2 X 10^{-3} M, and $[Br_2]_o$ = 5 X 10^{-5} M.

A (M) 10^{-4}		10^{-5}		10^{-6}		10^{-7}	
t sec	$[Br_2]$ X 10^5 M	t sec	$[Br_2]$ X 10^5 M	t sec	$[Br_2]$ X 10^5 M	t sec	$[Br_2]$ X 10^5 M
0	5.000	0	5.000	0	5.000	0	5.000
1	4.703	5	4.430	15	3.682	20	3.354
2	4.413	10	3.915	30	2.709	40	2.255
3	4.128	15	3.450	45	1.990	60	1.518
4	3.850	20	3.030	60	1.456	80	1.022
5	3.577	25	2.651	75	1.059	100	0.6875
6	3.311	30	2.307	90	0.7639	120	0.4617
7	3.049	35	1.997	105	0.5442	140	0.3091
8	2.794	40	1.716	120	0.3805	160	0.2060
9	2.543	45	1.462	135	0.2585	180	0.1362
10	2.298	50	1.232	150	0.1675	200	0.0889
11	2.058	55	1.023			220	0.057
12	1.823	60	0.0834				
13	1.592	65	0.0663				
14	1.467	70	0.0508				
20.54	0	91.05	0	200.4	0	317.5	0

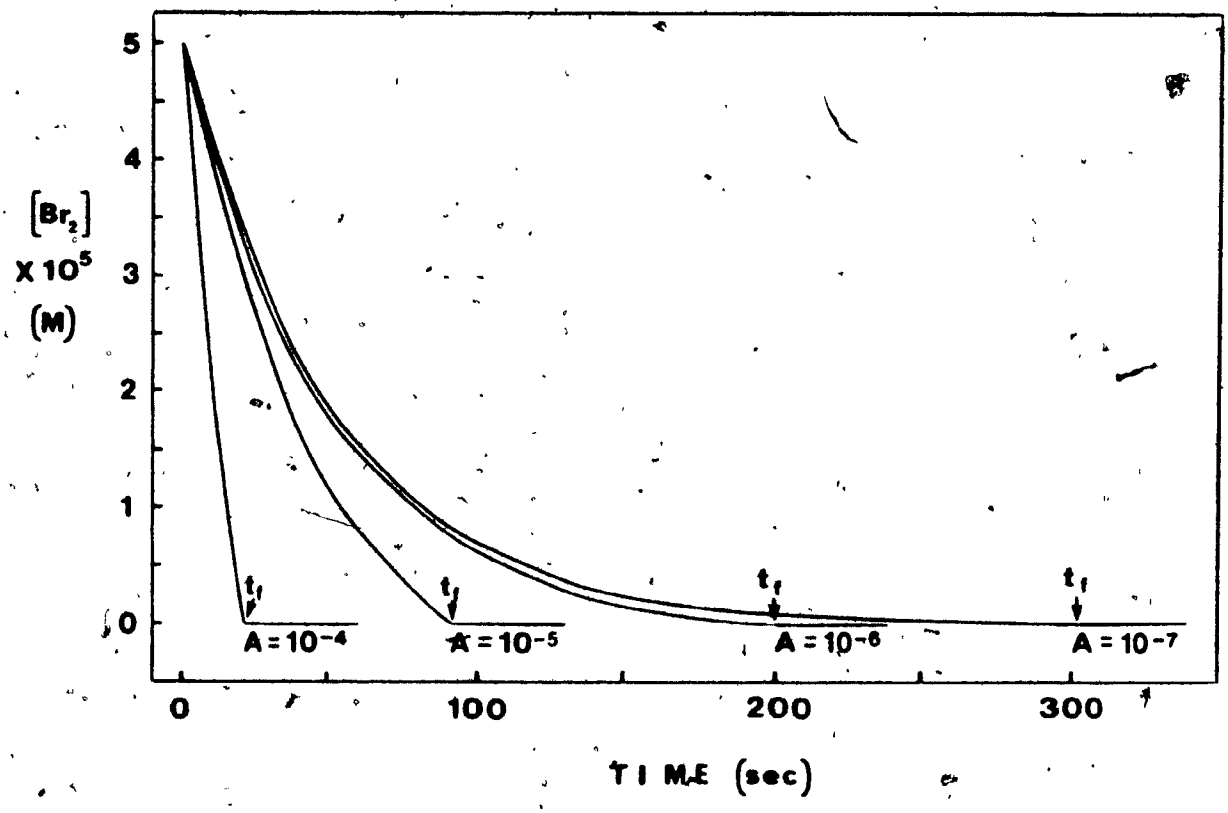


Figure 9. Theoretical plots of the data in Table VII. Compare the experimental traces of Figures 1-6. The integrated expression I.43 was used with $[P]_o = 2 \times 10^{-3}$ M, $[Br_2]_o = 5 \times 10^{-5}$ M, and B = 10 M^{-1} $sec.^{-1}$

The particulars which are readily perceptible in Figure 9 are firstly that for large values of A the overall order is zero as it should be since the rate expression I.43 reduces to:

$$\text{rate} = A\,B\,([P]_o - [Br_2]_o + [Br_2]) \qquad \text{I.49}$$

and for $[P]_o \gg [Br_2]_o$ the rate is constant. Secondly as the value of A

decreases, the rate approaches that for a first-order process. Thirdly, for values of A comparable to $[Br_2]_o$, the concentration of bromine reaches zero abruptly at a value defined as t_f. By contrast of Figure 9 with Figures 1-4, it can be said that the concept of reactivity of the substrate via the processes shown in Scheme III is valid. This is also corroborated with experimental data below (see Table IX).

To analyze for values of A and B, in practice, I.48 is approximated by equation I.50. Using k_1^{obsd} and t_f values, which can be obtained from the traces, A is estimated (I.50). B is calculated from equation I.51.

$$A = \frac{([P]_o - [Br_2]_o)[Br_2]_o}{[P]_o\{\exp(k_1^{obsd}t_f)\} - ([P]_o - [Br_2]_o)} \qquad \text{I.50}$$

$$B = k_1^{obsd}/([P]_o - [Br_2]_o) \qquad \text{I.51}$$

For continuity from the pseudo-zero order kinetics, $k_1^{obsd'}$ is given by equation I.52:

$$k_1^{obsd'} = Ak_1^{obsd}/([P]_o - [Br_2]_o) \qquad \text{I.52}$$

Notice that the calculated value of A (Table VIII) from equation I.50 may be lower by over 10%, but the calculated parameters, employed in the plots, such as $k_1^{obsd'}$ and B are less than 6% of the true values for $A < 10^{-4}$ (see Table VIII overleaf).

For values of A larger than 10^{-4}, the rate law reduces to zero-order (I.49, where $[P]_o >> [Br_2]_o$). From the foregoing, whenever such an order appears, the analysis of the data should be of a first-order type to minimize cumbersome calculations and retain high confidence level in the evaluated constants.

Table VIII. Comparison of A and B Values from Equation I.48 and from NEW1ST Program.[a]

$A^a \times 10^7$ M	B^a $M^{-1}sec^{-1}$	$(k_1^{obsd})^{b,c}$ $\times 10^2$ sec^{-1}	t_f^c sec	$A^d \times 10^7$ M	B^e $M^{-1}sec^{-1}$	$(k_1^{obsd'})^f$ sec^{-1}
1.00	10.0	1.969	317.5	0.941	10.1	0.950
10.0	10.0	1.976	200.4	9.47	10.1	9.60
100	10.0	2.007	90.05	93.0	10.3	95.7
1000	10.0	2.070	20.54	879	10.6	933

[a] Input of equation I.48. $[Br_2]_o = 5 \times 10^{-5}$ M, $[P]_o = 2 \times 10^{-3}$ M.

[b] Normal analysis using Swinbourne infinity value, gave correlation coefficients of 0.999999!

[c] Data from Table VII.

[d] Calculated values from I.50, [e] I.51, and [f] I.52.

pH 4-7

Table IX gives the experimentally calculated values of k_1^{obsd}, t_f obtainable from traces, A from equation I.50, and B from I.51 corrected for the presence of tribromide by the factor given earlier. Values of A are plotted as -log A versus pH in Figure 10. It can be said that 7 and 8 are reacting via their free base, since there can be no stable anion. The first term in the rate equation I.38 disappears and A takes the form:

$$A = k_1[H^+]/\{K_{a1}k_4\} \qquad I.53$$

and this plot should yield a slope of one.

The true test of the proposed mechanism was for the parent substrate. For low acid solution $k_3K_{a2} >> k_4[H^+]$, for equation I.43, and A is reduced to the following expression:

$$A = k_1[H^+]^2/\{K_{a1}K_{a2}k_3\} \qquad I.54$$

A plot of -log A versus pH therefore should yield a straight line of slope 2. This deduction is verified in Figure 10 for 4-pyrimidone.

Values of $k_1^{obsd'}$ obtained in this manner, are indicated as partially shaded symbols in Figure 8 and clearly show that the trend continues. Assuming that the mechanism in Scheme III is valid, a value of k_4 can be extracted for 7 and 8. The data showing attack of bromine upon the respective free bases of 1-methyl and 3-methyl-4-pyrimidone are plotted in Figure 11. The semi-shaded symbols represent the k_4 values extracted from analysis of equation I.51 and I.41, while open symbols are from simple exponential analysis. The constancy of the k_4 values over the range $5 < pH < 7$ corroborates the proposed mechanism. Thus, bromine attacks the free bases of 1-methyl and 3-methyl-4-pyrimidone with rate constants 15 $M^{-1}sec^{-1}$ and 8.5 $M^{-1}sec^{-1}$ respectively.

For the parent 4-pyrimidone, bromination occurs via a second-order process which varies linearly with pH. Table IX gives the data which are plotted in Figure 12. The unit slope is in agreement with equation I.41 where $K_{a2} << [H^+] << K_{a1}$. Also from Figure 10 k_4 is non-existent for 4, since the slope is 2 (see above discussion). Thus, the expression defining B in this pH region is $B = k_3K_{a2}/[H^+]$ which shows the reaction to be on the anion 12. The partially shaded symbols in

Figure 12 are derived from the mixed-order analysis discussed above. Their behaviour is also comparable to those obtained from first-order analysis illustrated as open symbols in the same figure. The rate constant of 4 via its anion is calculated to be 1.1 X 10^7 $M^{-1}sec^{-1}$ a value which is considerably less than that expected for the bromination of its covalent hydrate (an estimate is given later).

In summary, the data for all substrates over a wide range 0 < pH < 7 are explicable by the various mechanisms outlined in Scheme III and its rate law equation I.38.

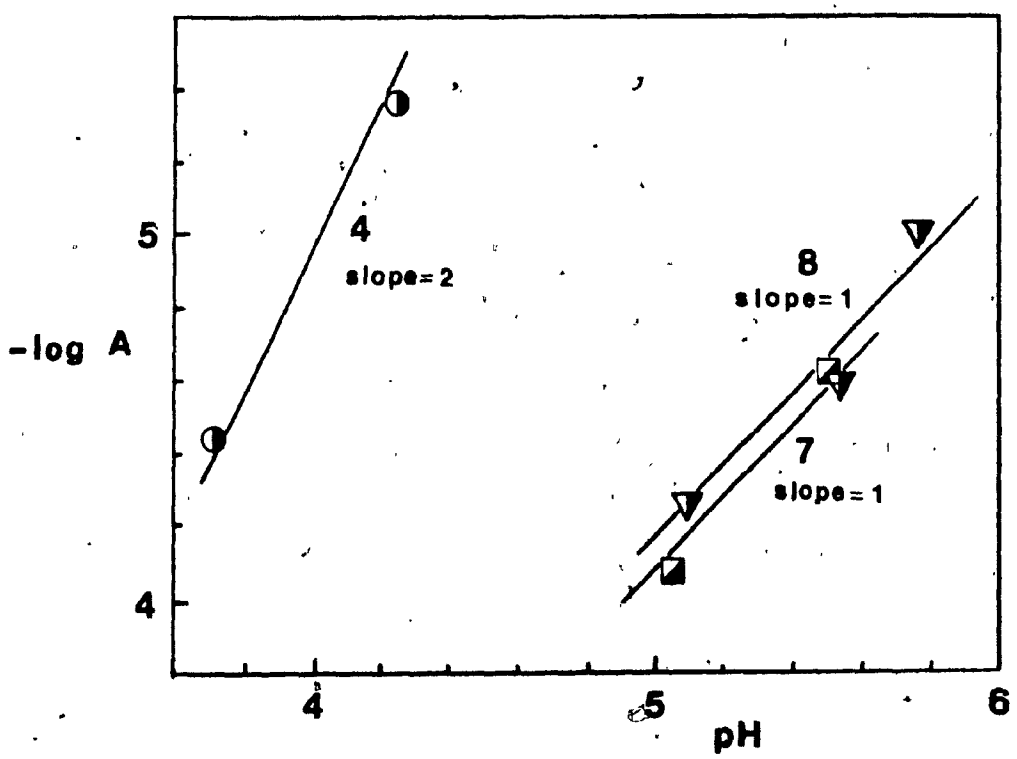


Figure 10. Relationships of - log A versus pH from equations I.53 and I.54 for 4-pyrimidone 4 (◑), 1-methyl-4-pyrimidone 7 (◪), and 3-methyl-4-pyrimidone 8 (▽).

Table IX. First and Second-order Rate Constants for the Bromination of 4-Pyrimidones at Low Acidity.[a]

4-Pyrimidone Derivative	pH	$[P]_o$ X 10^5 M	k_1^{obsd} X 10^3 sec^{-1}	t_f sec	A X 10^6 M	k_1^{obsd} X 10^4 sec^{-1}	k_2^{obsd} or B $M^{-1}sec^{-1}$
___ (4)	3.72	200	137	6.05	37.0[b]	26.0[c]	197[d]
		250	178	4.98	34.0[b]	24.6[c]	204[d]
	4.25	200	412	6.00	4.48[b]	9.46[c]	594[d]
		250	500	5.05	4.26[b]	8.69[c]	573[d]
	4.59	200	768				1130
		250	1000				1150
	5.03	200	2150				3100
		250	2670				3070
	5.55	50	1640				10300
		100	3500				10400
	5.73	100	3840				11500
	6.08	50	6430				41700
	6.25	50	7300				48300
		100	17200				53900
	6.44	50	13200				90000
1-Methyl ___	5.05	200	8.80	50.2	84.0[b]	3.78[c]	12.6[d]
(7)	5.50	150	7.18	153	23.7[b]	1.17[c]	13.9[d]
	6.02	100	6.37[e]				19.8[e]
3-Methyl ___	5.09	200	5.31	119	53.7[b]	1.46[c]	7.63[d]
(8)	5.53	200	4.81	223	25.1[b]	0.616[c]	6.91[d]
	5.76	200	6.16	290	9.77[b]	0.310[c]	8.86[d]
	6.44	200	6.71				9.65
	6.52	150	4.95				9.58
	6.84	200	5.91				8.51

[a] At 30°C, [KBr] = 0.100 M, I = 0.11 M, $[Br_2]_o = 5 \times 10^{-5}$ M. Each datum is the average of at least three runs all having a correlation coefficient of at least 0.9995.

[b] From equation I.49, [c] I.51, [d] I.50 and corrected for the presence of bromide ion equation I.21.

[e] $[Br_2]_o = 1.00 \times 10^{-4}$ M after mixing.

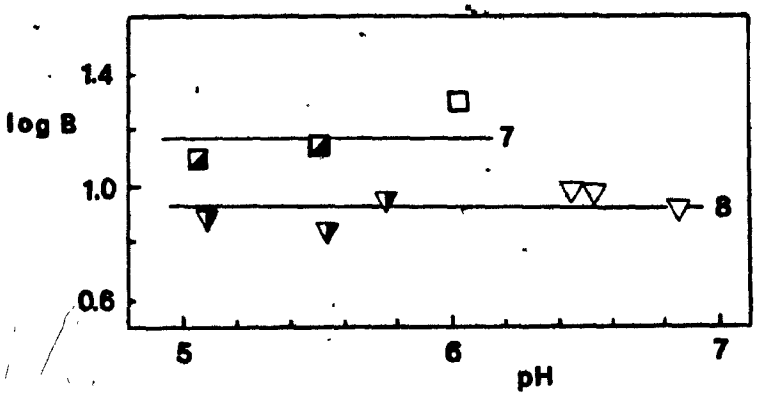


Figure 11. Rate profiles for 1-methyl-4-pyrimidone 7 (◪,□) and 3-methyl-4-pyrimidone 8 (▽,▽) showing constant rate of bromination of the free-base forms. Note partially shaded symbols indicate mixed order (from zero) analysis, while open symbols that from first order.

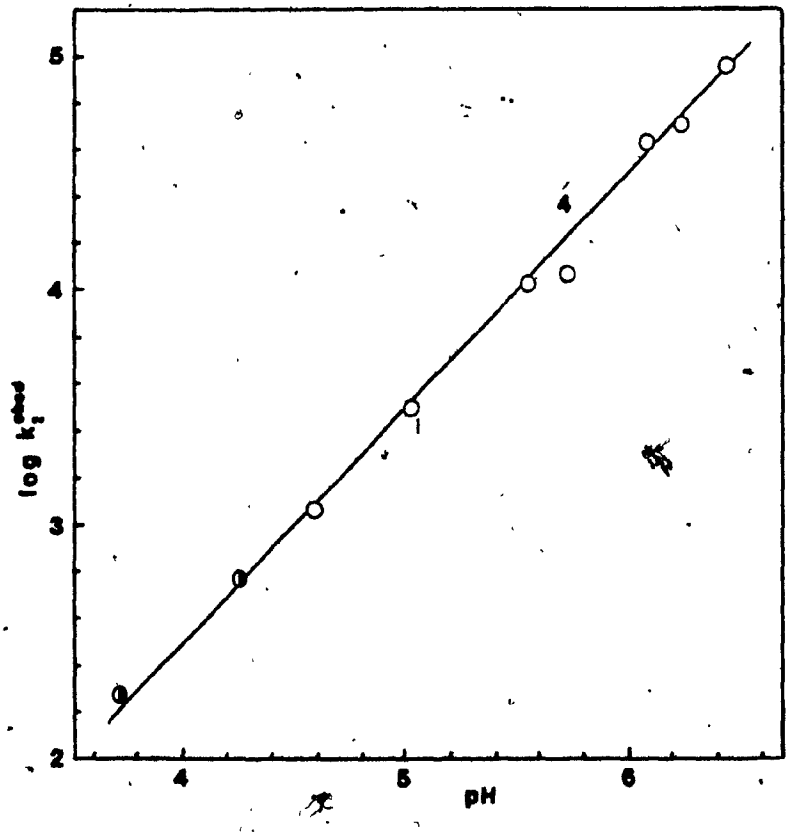
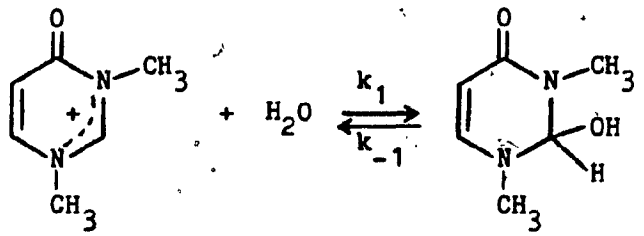


Figure 12. Log k_2^{obsd} versus pH for the bromination of 4-pyrimidoxide 12: mixed order (from zero) (◑) and first order (○) analyses.

Equilibrium Studies

In order to provide further support for the interpretation given above, the kinetics of equilibration[16,19] of the quaternary cation 10d and its pseudobase 14d (equations I.4, I.5, and I.55) were studied.



10d ⇌ 14d + H^+ (I.4)

$$\underline{10d} + {}^-OH \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} \underline{14d} \qquad \text{I.5}$$

$$\underline{10d} + H_2O + B \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} \underline{14d} + {}^+BH \qquad \text{I.55}$$

B in the last equation is the symbol for a general base. Let

$$k_f = k_1 + k_5[HO^-] + k_6[B] \qquad \text{I.56}$$

$$k_d = k_{-5} + k_{-1}[H^+] + k_{-6}[{}^+BH] \qquad \text{I.57}$$

then,

$$d[\underline{14d}]/dt = k_f[\underline{10d}] - k_d[\underline{14d}] \qquad \text{I.58}$$

It has been shown elsewhere[16] that this is a first-order process where:

$$k_1^{obsd} = (k_f + k_d) \qquad \text{I.59}$$

At equilibrium:

$$K_{R^+} = [\underline{14d}][H^+]/[\underline{10d}] \qquad \text{I.60}$$

and also

$$k_f[\underline{10d}] = k_d[\underline{14d}] \qquad \text{I.61}$$

Substitution of equations I.60 and I.61 into I.59 obtains:

$$k_1^{obsd} = k_f([H^+] + K_{R^+})/K_{R^+} \qquad \text{I.62}$$

After substitution of k_f from equation I.56:

$$k_1^{obsd} = \left\{k_1 + \frac{k_1[H^+]}{K_{R^+}} + \frac{k_5K_W}{K_{R^+}} + \frac{k_5K_W}{[H^+]}\right\} + \left\{\frac{k_6([H^+] + K_{R^+})K_a[B]_o}{(K_{R^+})(K_a + [H^+])}\right\} \qquad \text{I.63}$$

where K_W is the ionization constant for water (pK_W = 13.833 at 30°C) K_a is the dissociation for the base B and $[B]_o$ is the total concentration of the base B.

Values of k_1^{obsd} are tabulated in the second column of Table X. Rate constants k_f and k_d were calculated using $K_{R^+} = 2.95 \times 10^{-8}$ M, in column three and four of the same table and plotted in Figure 13. In the absence of much buffer ($\bar{I}$ = 0.01 M), equations I.56 and I.57 reduce to

$$k_f = k_1 + k_5[H^+] \qquad \text{I.64}$$

$$k_d = k_{-5} + k_{-1}[H^+] \qquad \text{I.65}$$

The last two equations describe the behaviour of the data plotted in Figure 13 for pH < 7.5. The curves shown herein were calculated using $k_1 = 0.2\ sec^{-1}$, $k_5 = 2.0 \times 10^7\ M^{-1}sec^{-1}$, $k_{-5} = 10\ sec^{-1}$, and k_{-1} =

7×10^6 $M^{-1}sec^{-1}$. The values of k_1 and k_{-1} are in reasonable agreement with $k_1 = 0.26$ sec^{-1} and $k_{-1} = 8.8 \times 10^6$ $M^{-1}sec^{-1}$ obtained from the bromination of 10d described earlier. This agreement provides strong support for the interpretation of the mechanism of bromination of 10d and, by implication, the other substrates also.

Table X. Rate Constants for Formation and Decomposition of the Pseudobase 14d.[a]

pH	k_1^{obsd} (sec^{-1})	k_f (sec^{-1})	k_d (sec^{-1})
4.72	122	0.200	121.8
5.02	70.6	0.200	70.4
5.25	43.4	0.200	43.2
5.47	30.1	0.300	29.8
5.69	22.6	0.300	22.3
6.09	14.7	0.500	14.2
6.21	12.0	0.550	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] = 0.10 M. Each datum is the average of three or more runs each with a correlation coefficient > 0.9995. The pK_{R^+} used to calculate k_f and k_d is 7.53. Ionic strength was 0.11 M.

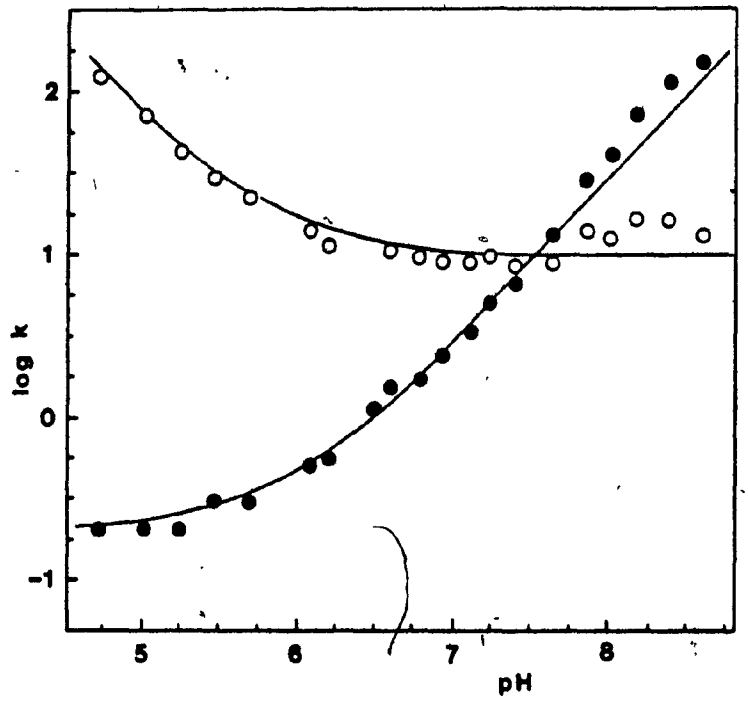


Figure 13. Plots of log k_f and log k_d versus pH for the formation (k_f, (●)) and decomposition (k_d, (O)) of the pseudobase 14d.

At pH > 7.5, the scatter of the data above the calculated curves, can be accounted for by the second term in equation I.63 which is due to general buffer catalysis in the formation of the pseudobase. There have been indications of such catalysis in other systems.[16,19,62,63]

Equation I.54 suggests a general-base assisted nucleophilic attack of water[63] upon the cation 10d and that the reverse reaction is general-acid catalyzed. Since both [B] and [BH^+] are proportional to $[B]_o$, the total buffer concentration at a given pH, this requires that k_1^{obsd} should be directly proportional to $[B]_o$. Table XI shows values of k_1^{obsd} obtained at various concentrations of the amine TRIS at four pHs in the region where the deviations are apparent in Figure 13. In each case k_1^{obsd} increased linearly with $[B]_o$, supporting the

involvement of buffer catalysis. These plots are displayed in Figure 14. As remarked earlier, the deviations for 8 in Figure 8 may also be due to buffer catalysis and, therefore, the operation of equation I.54.

Table XI. Buffer Catalysis Study for Formation and Decomposition of Pseudobase 14d.[a]

pH	[TRIS] M	[HBr] M	k_1^{obsd} sec^{-1}	pK_a of TRIS	Slope[b] $M^{-1}sec^{-1}$	Intercept[b] sec^{-1}
7.77	0.0317	0.0200	19.3	8.00		
	0.0238	0.0150	17.7	8.00		
	0.0119	0.00750	15.5	8.00	201	13.0
	0.00891	0.00562	14.7	8.00		
	0.00594	0.00375	14.2	8.00		
8.07	0.0489	0.0275	40.5	8.18		
	0.0367	0.0206	35.7	8.18		
	0.0275	0.0155	33.3	8.18	305	25.1
	0.0155	0.00870	30.1	8.18		
	0.00774	0.00435	24.4	8.18		
8.45	0.0733	0.0275	107	8.23		
	0.0550	0.0206	97.9	8.23		
	0.0275	0.0103	79.2	8.23	641	60.9
	0.0206	0.00773	73.7	8.23		
8.69	0.0800	0.0220	199	8.27		
	0.0600	0.0165	177	8.27	1120	110
	0.0300	0.00825	144	8.27		
	0.0225	0.00619	134	8.27		

[a] Same as footnote a in Table X.
[b] Taken from least square analysis.

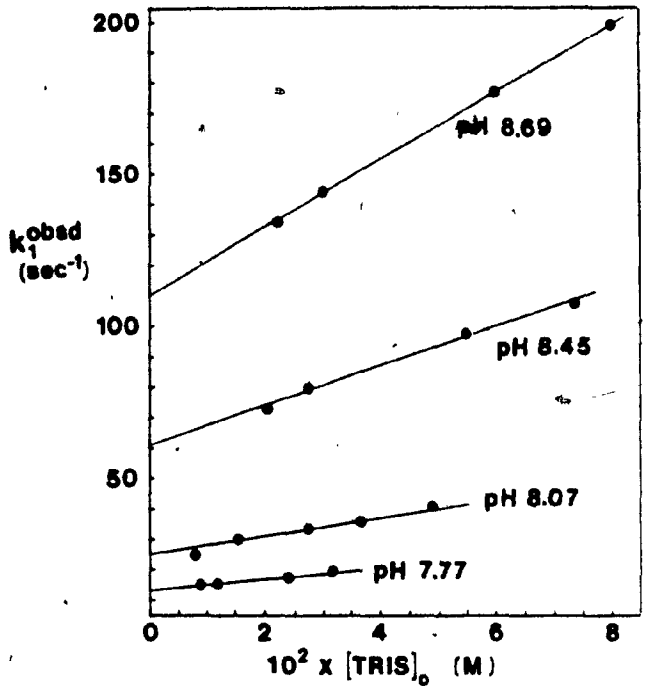


Figure 14. Variation of the rate constants k_1^{obsd} versus concentration of TRIS at different pHs.

The intercepts of the plots in Figure 14 (see Table XI) should behave as the first bracketed term of the function I.63. When a least square regression is performed on these intercepts, a good straight line is observed (Figure 15) with $k_5K_w = 2.2 \times 10^{-7}$ M sec^{-1} and $k_5 = 1.5 \times 10^7$ $M^{-1}sec^{-1}$, which is typical[16] for attack of hydroxide ion upon a quaternary heterocyclic cation. The intercept from such plot gave an absurd quantity for k_1: -6 sec^{-1}. This is perhaps not surprising when a number of unknown constants are to be found from regression analysis of a single set of data.

The slopes in Figure 14 (see Table XI) should obey the second bracketed term in equation I.63 as well. But as seen from this table, the pK_a value of TRIS is not constant probably due to changes in ionic

strength[61] or wrongly measured pHs. However, for a given ratio $[B]_o/[HBr]$ the pK_a value is constant. If K_a is also introduced as a varying parameter in equation I.63, assuming that the protonated form of the buffer equals the added amount of hydrobromic acid, then a plot of the slopes in Table XI versus $\{([H^+] + K_{R^+})K_a/(K_{R^+}([H^+] + K_a))\}$ should give a straight line of slope k_6. However, a poorly-defined (c-c = 0.950) line is obtained in Figure 16 from which k_6 was roughly estimated at $4 \times 10^3\ M^{-1}sec^{-1}$.

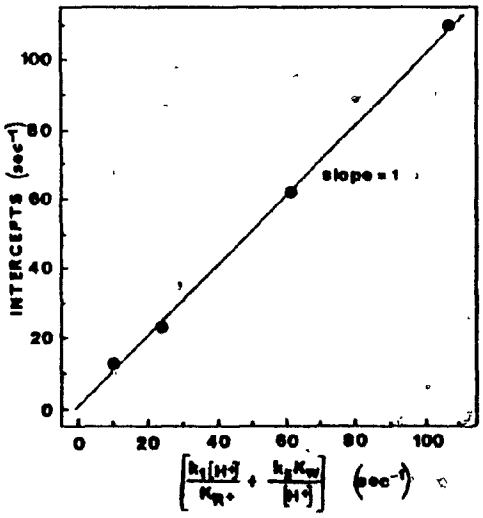


Figure 15. Plot of intercepts (Figure 14 and Table XI) versus $\{k_1[H^+]/K_{R^+} + k_5K_w/[H^+]\}$ of equation I.63.

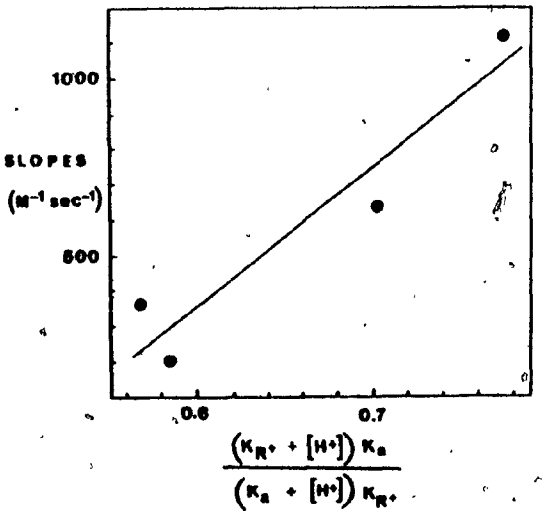


Figure 16. Plot of slopes (Figure 14 and Table XI) versus $\{((K_{R^+} + [H^+])K_a)/((K_a + [H^+])K_{R^+})\}$ of equation I.63.

It is suggested, by contrast with other buffer catalysis work that, since the data increase parabolically for $pK_a = 8.06$*, this effect is

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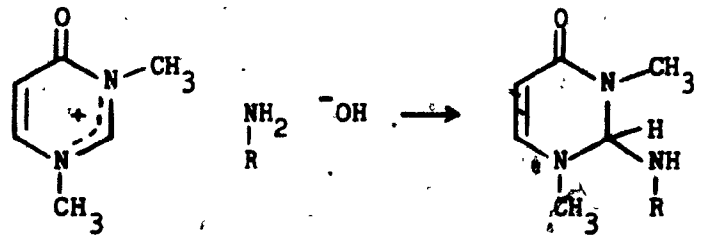
* This is the pK_a of TRIS[64] corrected for temperature and ionic strength.[61]

due to hydroxide catalyzed addition of the buffer forming 35.

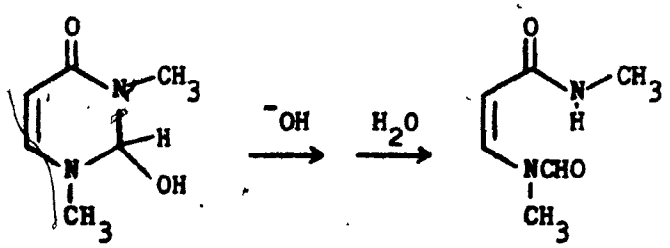


14d 35 I.66

RNH_2 in equation I.66 is the free-base component of TRIS. So far this mechanism has not been substantiated by further experiments.

The rate constant k_1, as discussed by Bunting,[16] represents water acting as a general base in equation I.4 and k_{-1} represents the hydronium ion acting as the general acid. On the other hand, k_5 likely corresponds to direct attack by hydroxide ion since there would be no thermodynamic advantage if it acted as a general base.[63,65]

It should be noted that while the pseudobase 14d is stable enough to permit observation[18d] and the kinetic experiments outlined above, it does undergo irreversible ring opening in alkaline medium. Preliminary study indicated that 14d disappeared with $k_1^{obsd} = 1.98 \times 10^{-3}$ sec^{-1} ($t_{1/2}$ = 350 sec) at pH 8.70. Assuming this was due to catalysis by hydroxide ion only, the second-order rate constant for this is 267 M^{-1} sec^{-1}. The disappearance of the 289 nm band of 10d was accompanied by the appearance of a new band ~260 nm which may have been due to the β-formamidoacrylamide derivative 36.

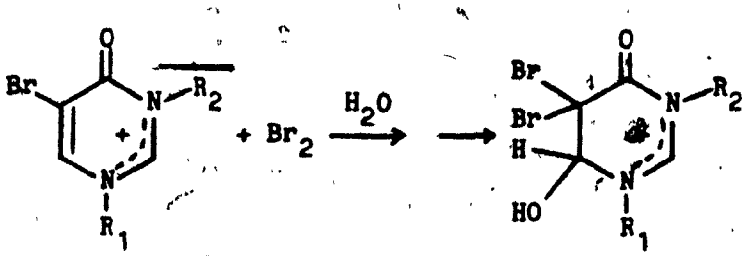


14d 36 I.67

At longer times the 260 nm band disappears presumably due to hydrolysis, as confirmed.[41a] A detailed study of this reaction is being carried out and the reaction sequence is outlined as 10d ⟶ ⟶ 16 (page 13).

Dibromination

In the earlier work of Banerjee[18c] the bromination of 31 (equation I.68) was said to produce a dibromo adduct which by analogy with the bromination of 5-bromo-2-pyrimidones, was assumed to be 37.[18c]

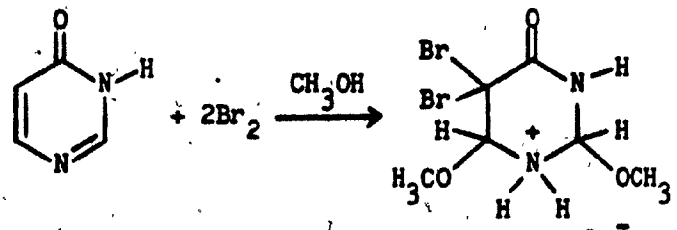


31 37 I.68

Unfortunately he was unsuccessful in the separation of 37. However, when 4-pyrimidone 4 and 5-bromo-4-oxo-pyrimidinium bromide (31, R_1=R_2=H) are reacted with two and one equivalent of bromine respectively in methanol, a stable crystalline substance is isolated. The procedure and

elemental analyses are given in the Experimental for compound 38 (equation I.69).

The proton NMR for this produet (38) in D_2O shows two methoxyls at 3.64 δ (s, 3) and 4.04 δ (s, 3), H-6 signal at 5.52 δ (s, 0.75) and 5.69 δ (s, 0.25), and H-2 signal at 8.28 δ (s, 0.25) and 8.55 δ (s, 0.75). The split intensities of the peaks assignable to H-2 and H-6 respectively are assumed to reflect the relative amount of the cis and trans isomers of 38. The ^{13}C NMR* in methanol also shows this peculiar 3:1 intensity ratio for carbons resonating above 87 ppm, but the methoxyl carbons are not easily distinguished because of solvent interference. Two N-D stretching frequencies at 2500 and 2310 cm^{-1} may be due to the presence of >N-D and $>N^{+}<^{D}_{D}$. Moreover, loss of aromaticity is inferred from the lack of absorption bands above 220 nm in the UV spectrum. Taking account of the mechanism outlined in Scheme II, it appears reasonable that the dibromination of 4 (equation I.69) leads to the cationic adduct 38.



4 38 I.69

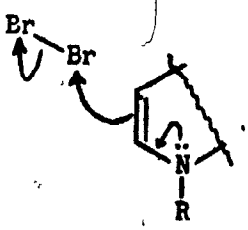
*Recorded by Dr. W. J. Chazin.

Quantitative Aspects

At this point the overall validity of equation I.11 and I.46 has been successfully demonstrated by analysis of the experimental results obtained from various pH regions. It is possible, by making estimates of k_2 for 4, 7, and 8 (equation I.11), to extract all the individual rate constants outlined for the process obeying this rate law. Moreover, estimates of the the extent of hydration were carried out and the results are summarized in Table XII.

For the species 10d all the individual rate constants can be extracted from bromination and equilibration studies. Such an analysis yields the value of $k_2 = 3.3 \times 10^9\ M^{-1}sec^{-1}$ for attack of bromine upon the pseudobase 14d. From the values of k_1 and K_{R^+}, k_{-1} is calculated as $8.8 \times 10^6\ M^{-1}sec^{-1}$ ($7 \times 10^6\ M^{-1}sec^{-1}$ from equilibration). Thus, all entries for 10d in Table XII are based firmly on experiment.

The estimation of other constants (k_1, and k_{-1}) in Table XII was done in the following way. Reaction of the pseudobase 14d with bromine is diffusion controlled (discussed in Chapter IV). There is no obvious reason why the bromination of the other substrates should not be also particularly since the driving force for the bromination is simply the lone pair on the nitrogen atom of the enamine (depicted below) and similar for the different adducts.



Arguments for choosing different estimates of k_2 would imply that the diffusion-controlled rates for very similar substrates should be different. However, as is shown for phenols and pyridones in Chapter IV, the diffusion-controlled rate constant is similar! Thus, k_2 is approximated at 3.3×10^9 $M^{-1}sec^{-1}$ for 4-pyrimidone and its derivatives.

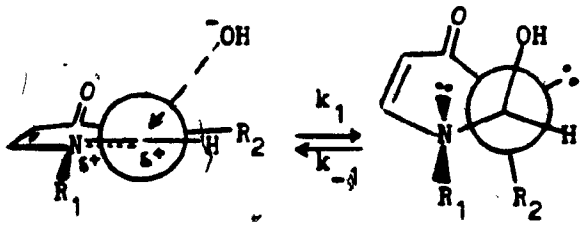
The value of k_4 (Table XII) for reaction of the free base of 4-pyrimidone with bromine cannot be obtained from kinetic studies due to the fact that the reaction of the anion was much faster even at pH 3.72. However, an upper limit can be estimated. The lowest rate for reaction of this substrate via its covalent hydrate is $k_1^{obsd'} = 9 \times 10^{-4}$ sec^{-1} at pH 4.25. Thus, the second-order rate for direct attack of bromine upon 4 must be less than 2×10^{-6} $Msec^{-1}$.

$$\text{rate} = k_4[4][Br_2]_o < 2 \times 10^{-6} \text{ Msec}^{-1} \qquad \text{I.70}$$

Insertion of the appropriate concentrations into equation I.70 leads to the conclusion that $k_4 < 20$ $M^{-1}sec^{-1}$ for direct attack upon 4. If the same trend of reactivity as their covalent adducts is assumed, then the value of k_4 for 4 should be between that of 7 and 8 with an estimate of 11 $M^{-1}sec^{-1}$.

The value of k_1 in Table XII ought to be constant (and it is) since this reflects the similarity in the angle of approach of the hydroxide on a planar molecule in the formation of the pseudobase from its conjugate acid (see below) which is independent of interactions from R_1, R_2, and the lone pairs as is the case in the adduct. Such interactions are the driving force for the rate of decomposition (k_{-1}) of the pseudobase or covalent hydrates. Unfortunately k_{-1} is not

calculable from the bromination kinetics of the covalent hydrates.



+ other conformers

However, the overall forward rate of bromination ($k_2K_{R^+}$) shows the similarity in reactivity between 4 and 8 and between 7 and 10d. This, and other constants in Table XII, indicate, perhaps weakly, that the preferential protomer of 4-pyrimidone is the lactam form 3,4-dihydro-4-(3H)-pyrimidone 4.

Table XII. Summary of Constants from Bromination (and Equilibration) for 4, 7, 8, and 10d.[a]

Constants (units)	Substrates 4	7	8	10d
k_1k_2/k_{-1} (sec^{-1})	40.b	121	21.3	97.5
k_1 (sec^{-1})	0.24	0.32	0.15	0.26 (0.2)
k_2 ($M^{-1}sec^{-1}$)	~3.3×10^9	~3.3×10^9	~3.3×10^9	3.3×10^9
k_{-1} ($M^{-1}sec^{-1}$)	~2.0×10^7	~8.7×10^6	~2.3×10^7	8.8×10^6 (7×10^6)
$K_{R^+} = k_1/k_{-1}$	~1.2×10^{-8}	~3.7×10^{-8}	~6.5×10^{-9}	2.95×10^{-8}
pK_{R^+}	~7.9	~7.4	~8.2	7.53
pK_1 (fitted)	1.80	2.00	1.87	—
pK_1 (lit.)[b]	1.85	2.02	1.84	—
K_{R^+}/K_1	~8.0×10^{-7}	~3.7×10^{-6}	~4.6×10^{-7}	—
k_3 ($M^{-1}sec^{-1}$)	1.1×10^7	—	—	—
k_4 ($M^{-1}sec^{-1}$)	~11	15	8.5	—

[a] Refer to Scheme III for the significance of the rate constants. Numbers in brackets are from equilibrium study, while those preceded by (~) are estimates (see text).
[b] See Table II.

2-PYRIMIDONE AND ITS DERIVATIVES

The data for this series of compounds are reported on Tables XIII-XV and are interpreted for small pH intervals as was done for 4-pyrimidone above. Data for 9d were taken from the literature.[19] Figures 5 and 6 give the experimental traces which are comparable to those of the 4-pyrimidones and lend support to the same mechanism.

pH 0-2

The raw data are presented in Table XIII. No deviation from linearity was observed at high acidity for the two compounds 2 and 6 as can be seen from their plots of log k_2^{obsd} versus pH (see Figure 17), although an expanded scale plot of the same data at I = 1.1 M and I = 0.11 M, shows a negative ionic strength effect of 1.2. The linearity supports further the reaction via the respective adducts even at pH 0. The data in this pH region are entirely consistent with equation I.31 for 2-pyrimidone and 1-methyl-2-pyrimidone. The dimethyl compound obeyed equation I.33. The experimental points depicted in solid symbols were obtained from mixed-order analysis equation I.28 and I.29.

By analogy to the behaviour of the 4-pyrimidinones, it can be concluded that the 2-pyrimidones also are reacting via their respective covalent hydrates 13a-c and pseudobase 13d. Earlier studies afforded spectroscopic evidence of the pseudobase 13d[19] and 23d[18b] and the ultimate products 25.

The values employed to draw the rate profiles of Figure 17 were k_1k_2/k_{-1} = 2000 sec^{-1} for 2, 540 sec^{-1} for 6, and 135 sec^{-1} for

9d. For the last substrate the value of k_2 was calculated to be 2×10^9 $M^{-1}sec^{-1}$.

Table XIII. Second-order Rate Constants for the Reaction of Bromine with 2-Pyrimidones 2 and 6 at High Acidity.[a]

2-Pyrimidone Derivatives	pH	$[P]_o \times 10^6$ M	k_1^{obsd} sec^{-1}	$k_2^{obsd} \times 10^{-3}$ M^{-1} sec^{-1}
___ (2)	-0.035[b,c]	2000	0.140	1.50
	0.264[b,d]	2000	0.285	3.16
	0.614[b,e]	2000	0.658	6.96
	0.908[b,f]	2000	1.37	14.6
	0.96	500	2.74	17.1
		954	5.44	16.9
	1.22[g]	2000	2.65	28.3
	1.55	1000	19.3	57.0
		2000	39.5	56.8
	1.99	1000	51.7	153
		2000	106	152
	2.52	1000	113[h]	461
	2.99	1000	156[h]	461
		2000	318[h]	457
	3.51	1000	154[h]	455
1-Methyl ___ (6)	-0.035[b,c]	2000	0.0371	0.396
	0.264[b,d]	2000	0.0714	0.792
	0.614[b,e]	2000	0.173	1.83
	0.908b,f	2000	0.365	3.89
	0.97	1000	1.62	5.09
		2000	3.36	5.14
	1.22[g]	2000	0.755	8.05

Table XIII. Continued.

2-Pyrimidone Derivatives	pH	$[P]_o \times 10^6$ M	k_1^{obsd} sec^{-1}	$k_2^{obsd} \times 10^{-3}$ $M^{-1} sec^{-1}$
1-Methyl ___	1.50	1000	5.49	16.2
		2000	11.2	16.1
	1.97	1000	13.7	40.5
		2000	28.5	41.0
	2.21	1000	23.7	70.0
		2000	48.4	69.6
	2.42	1000	33.4[h]	98.6
		2000	67.3[h]	96.8
	2.90	1000	48.6[h]	144
		2000	98.9[h]	142
	3.12	1000	57.9[h]	171
		2000	119[h]	171
	3.83	1000	71.2[h]	210

[a] At 30°C, $[Br_2]_o = 5.00 \times 10^{-5}$ M., [KBr] = 0.10 M, I = 0.11 M. Each datum is the average of at least three runs all giving a correlation coefficient greater than 0.9997 except where noted otherwise.

[b] pH = -log[HBr].

[c] ([HBr] + [KBr]) = 1.100 M, [d] 1.144 M, [e] 1.088 M, [f] 1.098 M, [g] 1.097 M.

[h] k_1^{obsd} from mixed-order analysis (c-c > 0.999). See text.

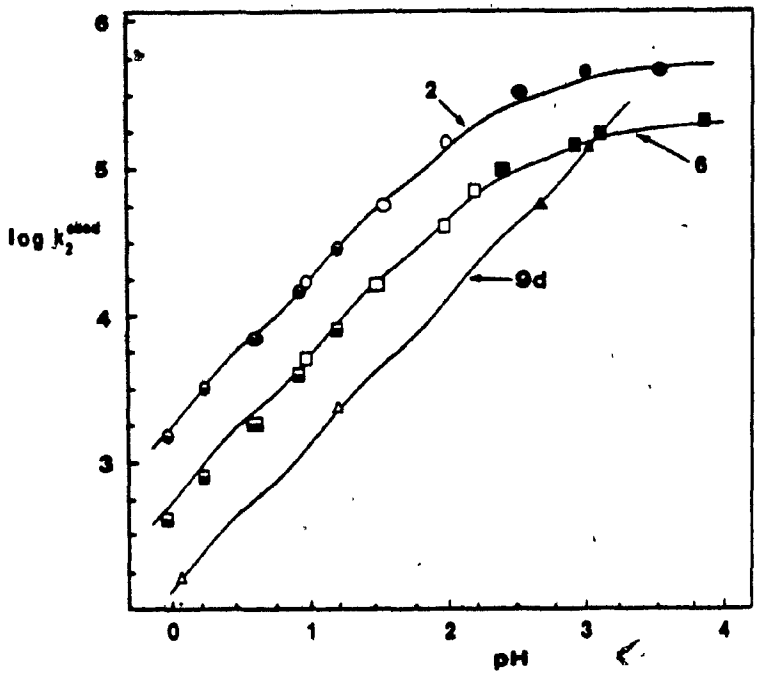


Figure 17. Rate profiles at high acidity for the bromination of 2-pyrimidone 2, 1-methyl-2-pyrimidone 6, and 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrosulphate 9d.[19] The semi-shaded symbols (⊖, ⊟) are at 1.1 M ionic strength all others at 0.11 M ionic strength. The second-order rate constants were obtained from pseudo-first-order (⊖,○,⊟,□,△) and mixed-order (●,■,▲) analysis.

pH 2-3

In this pH range the full rate equations I.28 and I.29 were used to extract the values of k_2^{obsd} (Table XIII) plotted as solid symbols in Figure 17. Also k_1^{obsd} were obtained from this analysis and plotted as closed symbols in Figure 18. The curvature of the plots is due to the pK_a for each species being close to the pH values. The fitted pK_as agreed to the spectrophotometric pK_as found in the literature (see Table II).

For 9d no such pK_a exists and the rate profile continues to be a straight line of unit slope (equation I.29).

Table XIV. First-Order Rate Constants for the Reaction of Bromine with 2-Pyrimidones 2 and 6 at Low Acidity.[a]

2-Pyrimidone Derivative	pH	$[P]_o$ X 10^5 M	k_o^{obsd} X 10^5 M^{-1} sec^{-1}	k_1^{obsd}, sec^{-1}
___ (2)	2.52	100	387[b]	3.87
	2.99	100	185[b]	1.85
		200	366[b]	1.83
	3.51	100	84.5[b]	0.845
	4.00	100	27.5	0.275
		200	56.4	0.282
	4.52	100	11.4	0.114
		200	22.8	0.114
	5.00	100		0.0308[c]
		200		0.0311[c]
	5.48	100		0.0103[c]
		200		0.0107[c]
1-Methyl ___ (6)	2.42	100	283[b]	2.83
		200	558[b]	2.79
	2.90	100	133[b]	1.33
		200	266[b]	1.33
	3.12	100	106[b]	1.06
	3.83	100	21.9	0.219
		200	43.3	0.217
	4.53	100	6.14	0.0614
		200	12.4	0.0620
	5.00	100	2.04	0.0204
		200	4.14	0.0207
	5.45	100	0.736	0.00736
		200	1.54	0.00770
	5.87	100		0.00331[c]
	6.02	100	0.263	0.00263
	6.44	200		0.000616[c]

[a] As footnote a Table XIII.
[b] From mixed-order analysis (σ-σ > 0.999). See text.
[c] From second type of mixed-order analysis. See Table XV.

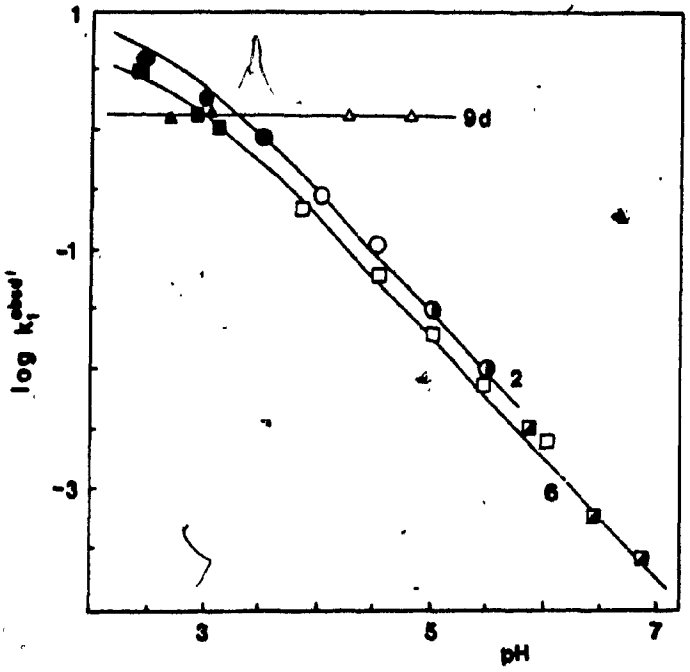


Figure 18. Variation of $k_1^{obsd'}$ with pH for the bromination of 2-pyrimidone 2, 1-methyl-2-pyrimidone 6, and 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium hydrosulphate 9d. The different symbols represent constants extracted from mixed-order (●,■,▲) (following first-order), zero-order (○,□,△), and mixed-order (◐,◪) (following zero-order) analysis.

pH 3-7

The significant rate constants are tabulated in Table XIV and plotted in Figure 18 (see above). The solid symbols represent values from mixed-order analysis and the open symbols were obtained from pseudo-zero-order analysis.

To this pseudo-zero-order kinetic behaviour is gradually superimposed a pseudo-first-order process leading to a second type of mixed-order analysis. The process outlined in Scheme III is also applicable to the 2-pyrimidone and its N-methyl derivative. Its rate law was discussed at length previously. Application of equation I.46

leads to the calculation of k_1^{obsd} (equation I.51) whose values are superscripted c in Table XIV and plotted as semi-closed symbols in Figure 18. The best-fit curves in this figure are drawn utilizing the same pK_as of Figure 17 and yielded k_1 value of 11 $\pm$ 2 sec^{-1}, 5.0 $\pm$ 0.7 sec^{-1}, and 1.3 sec^{-1} for 2, 6, and 9d respectively. These data are thus consistent with equation I.51.

To discern whether the free base or the anion of 2-pyrimidone and 1-methyl-2-pyrimidone was reacting at higher pHs, the A values of Table XV were plotted as -log A versus pH in Figure 19. As discussed earlier a slope of two would imply, from equation I.53, that bromination occurs via the anion, while a slope of one would imply reaction via the free-base form (equation I.52). It turns out, that 2-pyrimidone reacts via its anion at pH 5.00 while 1-methyl-2-pyrimidone undergoes reaction upon its free-base form.

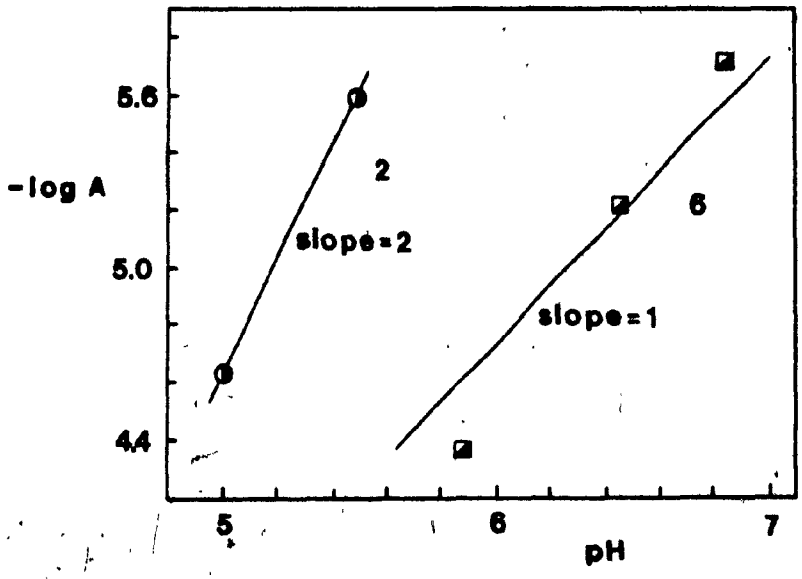


Figure 19. Relationships of -log A versus pH from equations I.53 and I.54 for 2-pyrimidone 2 (●) and 1-methyl-2-pyrimidone 6 (◪).

The magnitude of the rate constant k_4 (see Scheme III) for 6 was estimated from the values of B (Table XV), according to equation I.50 and plotted in Figure 20. At pH 6.84, only the last 15% of the trace was analyzed as first-order. It is evident from Figure 6 that there is an initial fast process followed by a slower one. Other traces at different pHs show that this process increases as the acidity is lowered. At this point speculation points to bromination occurring on some other form of the substrate. This intermediate also enhances the apparent reactivity of 1-methyl-2-pyrimidone leading to the deviation shown in Figure 20 above the calculated line. The horizontal line indicates $k_4 = 250\ M^{-1}sec^{-1}$.

For the parent substrate no such anomaly was observed; however, the very rapid disappearance of bromine did not permit further study beyond pH 6.3. The experimental points from both mixed-order analysis and pseudo-first-order analysis follow a straight line of unit slope. This second-order bromination of 2-pyrimidoxide ion 11 has a rate constant of $5.1 \times 10^7\ M^{-1}sec^{-1}$. The results are listed in Table XV and represented in Figure 20.

Table XV. Second-order Rate Constants for Bromination of 2-Pyrimidones at Low Acidity by Mixed-order[a] and First-order Analysis.[b]

2-Pyrimidone Derivative	pH	$[P]_o$ X 10^5 M	k_1^{obsd} sec^{-1}	t_f sec	A X 10^6 M	$k_1^{obsd'}$ X 10^3 sec^{-1}	B M^{-1} sec^{-1}
___ (2)	5.00[a]	100	1.31	0.858	24.5	30.8	3860
		200	2.49	0.437	24.4	31.1	3580
	5.48[a]	100	3.95	0.760	2.48	10.3	11700
		200	7.64	0.384	2.75	10.7	11000
	5.73	100	6.13				18400
	6.01	100	10.4				31800
		200	21,1				31400
	6.25	100	18.0				56200
1-Methyl ___	5.87[a]	100	0.0753	9.70	42.0	3.31	222
(6)	6.44[a,c]	200	0.201	11.0	6.00	0.619	290
	6.84[a,d]	200	0.274	12.0	1.88	0.265	394

[a] Some of this data is also shown in Table XIV.

[b] $[Br_2]_o$ = 5.00 X 10^{-5} M after mixing. Solutions were 0.10 M in KBr at 30°C with a buffer strength of 0.01 M. Each datum is the average of at least three runs each with a correlation coefficient > 0.9995.

[c] Only the last 50% of the traces were analyzed.

[d] Only the last 15% of the traces were analyzed. See text.

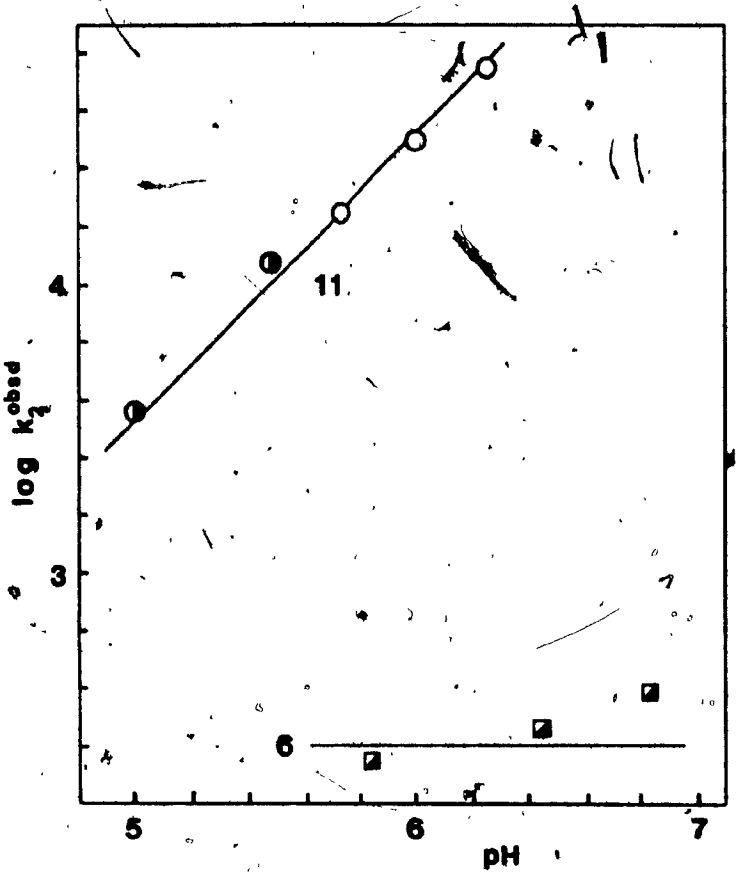


Figure 20. Log k_2^{obsd} versus pH for the bromination of 2-pyrimidoxide 11 and 1-methyl-2-pyrimidone 6: mixed-order (◑, ◪) and first-order (○) analyses.

Quantitative Aspects

The order of reactivity for this series of compounds is 2 > 6 > 9d. This is a complete reversal for what was observed in the 4-pyrimidones vis-a-vis substitution.

On the basis that experimental data are compatible with the mechanism outlined in Scheme III, it is possible to consider the magnitudes of the various rate constants and estimate the degree of

hydration.

The pertinent bromination and equilibration rate constants for 9d were determined by Tee, Thackray, and Berks.[19] They found K_{R^+} = 6.92 X 10^{-8} M and k_2 = 2 X 10^9 $M^{-1}sec^{-1}$. The relative rates for attack of bromine on the covalent hydrates may be estimated in the following way. Firstly, addition of bromine is always α to a tertiary hydroxyl group. Thus, the value of k_2 should be relatively independent of the two possible adducts at C-4 or C-6, although it has been shown earlier[47] in equation I.7, that for unsymmetrical quaternary 2-pyrimidone cations, adduct formation occurred preferentially α to the nitrogen bearing the smaller substituent.[47] Also applying similar reasoning as for the 4-pyrimidones, the diffusion-controlled bromination rate for the dimethyl cation 9d (2 X 10^9 M^{-1} sec^{-1}) should be the same for all the 2-pyrimidones. A list of these rate constants is given in Table XVI.

2-Pyrimidone does not react via its free-base form 2. If it did the rate constant for attack of bromine upon 2 (i.e. k_3) may be estimated in the following way. At pH 5.00 k_2^{obsd} = 3.57 X 10^3 $M^{-1}sec^{-1}$ and 2 is reacting via its anion, which places any reaction rate via its free base at $k_3 < 3600$ $M^{-1}sec^{-1}$. Probably the same value k_3 = 250 $M^{-1}sec^{-1}$ as for 1-methyl-2-pyrimidone is reasonable because these two compounds react similarly throughout the pH range.

Table XVI. Summary of Rate Constants for the Reaction of Bromine with 2-Pyrimidone 2, the 1-Methyl Derivative 6, and the Cation 9d.[a]

Constants	Units	Substrates 2	6	9d
k_1k_2/k_{-1}	sec^{-1}	1900	550	135
k_1	sec^{-1}	11	5.0	1.3
k_2/k_{-1}		170	111	104
k_2	$M^{-1}sec^{-1}$	~2×10^9	~2×10^9	2×10^9
k_{-1}	$M^{-1}sec^{-1}$	~1.2×10^7	1.8×10^7	2×10^7
K_{R^+}	M	~9.5×10^{-7}	~2.7×10^{-7}	6.92×10^{-8}
pK_{R^+}		~6.0	~6.6	7.16
pK_1 (fitted)		2.44	2.58	—
pK_1 (lit.)[b]		2.24	2.50	—
K_{R^+}/K_1		~2.1×10^{-4}	~9.5×10^{-5}	—
k_4	$M^{-1}sec^{-1}$	~250	250	—
k_3	$M^{-1}\ sec^{-1}$	5.1×10^7	—	—

[a] See Scheme III for description of rate constants.

[b] See Table II.

Summary for the Pyrimidones

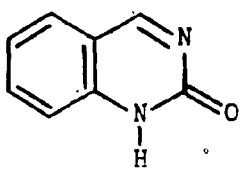
The values of k_1 for 4-pyrimidones are almost two orders of magnitude less than those of the 2-pyrimidones. This significant difference can perhaps be rationalized by the conjugate acids of 2-pyrimidones which have the positive charge delocalized over four ring atoms compared to three for the conjugate acids of 4-pyrimidones, making them "softer" acids. This then favours the formation of the "soft" base: covalent hydrate or pseudobase. Moreover, aqueous adducts are

formed only at C-2 for the 4-pyrimidones. This statistical factor of two is also responsible for the overall decrease in the magnitude of k_1 for 4-pyrimidone relative to the 2-pyrimidones.

In both sets of compounds the rate constant for the acid-catalyzed decomposition of the covalent hydrate and pseudobase is roughly estimated at 10^7 $M^{-1}sec^{-1}$. This is consistent with the idea that protonation is influenced little by steric effects.

Adducts form less readily for the 4-pyrimidones than for 2-pyrimidones (compare K_{R^+} values Table XII and XVI). The fact that there are less adducts in solution per mole of substrate decreases the apparent rate of bromination. Moreover, it increases the possibility that some other form of the substrate may react competitively with the covalent hydrate or pseudobase.

Quantitative approximations set the extent of covalent hydration, defined by the ratio K_{R^+}/K_1 (Tables XII and XVI) at ~0.0001% for 4-pyrimidones. That for the 2-pyrimidones is about one hundred times greater at ~0.01%. A generalization may be made at this point concerning covalent hydration: the more stable the conjugate acid, the greater the extent of hydration. In fact, 2(1H)-quinazolinone 39 exists to the extent of 25% as its covalent hydrate[102] (i.e. $K_{R^+}/K_1 = 0.33$). Thus, relative to 2-(1H)-pyrimidone 2 there is ~1000-fold more hydration ($\Delta(\Delta G)$ = 4 Kcal/mole) in the case of 39.



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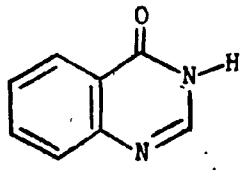

40

The degree of covalent hydration of 4(3H)-quinazolinone 40 is not known,[a,54] although its covalent hydrate is involved in its bromination in aqueous solution.[54] Thus, comparison between 4 and 40 is not possible at this time.

Conclusions

In aqueous solution 2- and 4-pyrimidones react via the pathway shown in Scheme III (page 43). At high acidity pH < 3 the process defined by equation I.12 is dominant in the rate law. Although a very limited amount of covalent hydrate (pseudobase) is present, its high reactivity $k_2 > 10^9$ $M^{-1}sec^{-1}$ facilitates bromination of these substrates. Indeed, at pH > 2 formation of the adducts from the conjugate acids is the rate-determining step, whereas at pH < 2 attack of bromine upon 13 or 14 is rate-limiting.

At pH > 3, the apparent reactivity of the covalent hydrates decreases linearly with pH due to the decrease in conjugate acid concentration above the protonation K_{a1} of the substrates. Consequently, for substrates not containing an ionizeable hydrogen, except for the quaternary salts, undergo bromination via the respective free-base forms. The parent substrates, on the other hand, reacted via their anionic forms 11 and 12 with rate constants of $\sim 10^7$ $M^{-1}sec^{-1}$.

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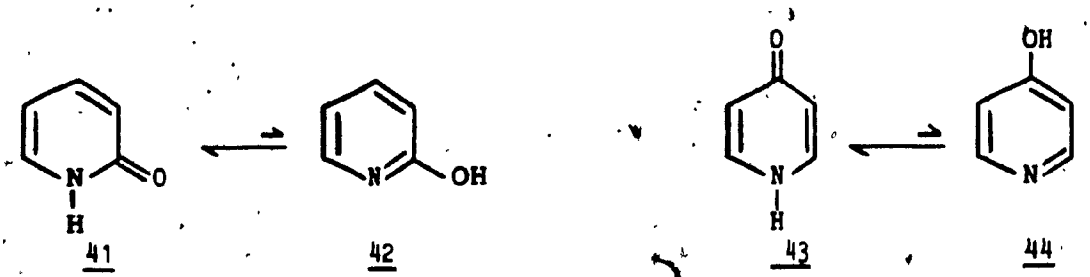
[a] Estimation of the degree of covalent hydration of 40 from bromination data is not possible due to lack of a reasonably accurate value of K_{R^+} for its dimethyl derivative.

These results demonstrate quite dramatically the effect that covalent hydrates may have upon reactivity. For the pyrimidoxides the reactivity is reduced ~100-fold compared to the respective covalent hydrate. In many cases anionic reactivity (see later) is diffusion controlled (~7 X 10^9 $M^{-1}sec^{-1}$) in aqueous solution. For the N-methyl derivatives covalent hydrates increase the second-order rate constant by a factor 10^7-10^8 compared to the rate constant for attack of bromine upon the free-base forms.

II. THE PYRIDONES

The systems, 2- 41 and 4-pyridone 43 and their respective tautomers 42 and 44 are the prototypes for the prototropic tautomerism that may be shown by many heterocyclic systems.[26]



41 42 43 44

Extensive studies on tautomeric equilibria in gas phase[68] and in solution,[20b,66-68,79b] have asserted the predominant lactim 42 or 44 and lactam 41 or 43 form respectively. Such studies on the static systems, however, cannot differentiate between the reactivities of the two tautomers (lactam and lactim). Therefore, bromination was chosen to study the dynamics of these systems and elucidate the main features of the reaction.

The object of this work was firstly to ascertain what are the reactive forms of the tautomeric system. Thus, suitable N- and O-methyl derivatives were also studied for comparison. Perusal of the literature[69] does not clarify the preferred orientation of the

bromination in the unsymmetrical 2-pyridone system. Another object of this study was to uncover the preferential (if any) reactive site. To this end, the kinetics of bromination of the 3- and 5-bromo and respective N-methylated derivatives were also carried out.

Pyridones, much like the pyrimidones, are amphoteric. It was thus important to ascertain whether the cation, the free-base, or the anion is the reacting entity at a specific pH's. This was made possible by comparison of the various rate profiles with those of the appropriate model derivatives.

The halogenation of the pyridones occurs very easily,[69] and kinetic complications were to be expected from dibromination. This problem led to the derivation of the consecutive second-order kinetic analysis and solution as outlined in the appendix. For such a study the kinetics of the monobromo derivatives were also needed. Apparently the speed of the bromination reaction has precluded kinetic studies by conventional means. However, the stopped-flow method was successfully applied to the study of the pyridones in the present work.

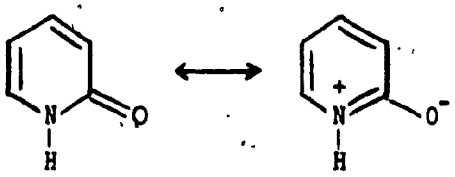
Lastly, it was desired to correlate the anionic rate constants to the number of aza nitrogens. This is in fact an issue of Chapter IV and requires no further comment at the moment.

STRUCTURE OF THE PYRIDONES

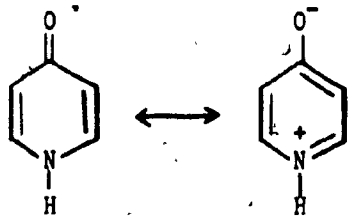
Tautomerism

The aromatic 2- and 4-pyridones do not have the properties of simple unsaturated lactams.[70] It has been estimated that 2-pyridones have about 35% of the aromaticity of benzene as defined by their ability to sustain an induced ring current[71] and as calculated by the SCF treatment.[72]

The infrared spectra of 2- and 4-pyridones are consistent with the lactam structures 41 and 43.[73] The contribution of the dipolar form 45 or 46, as studied by ^{18}O labelled compounds, was found to be minimal. Comparison of IR and Raman spectra of 43 with those of 4-pyrimidinium ions and rationalization of the dipole moment, has led to the estimate that the upper limit of the contribution to 43 by 46 is 10 to 15%.[74]



41 45



43 46

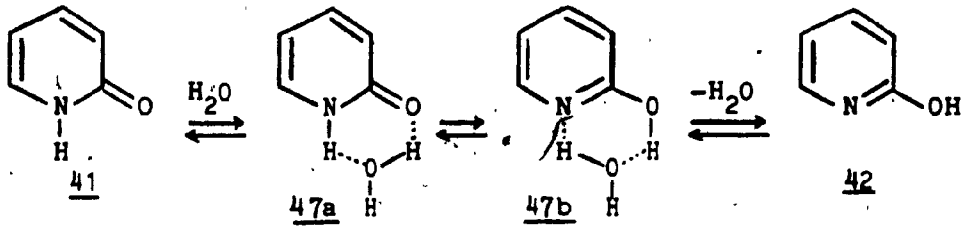
The UV spectrum of 2-pyridone in water indicates that it exists as the amide tautomer 41 (> 99%).[20b,66,67,79b] The lactam form of 4-pyridone (43) was deduced from NMR studies in aqueous solution.[75] In deuteriochloroform a very fast intramolecular exchange was shown by the ionizeable hydrogen of 43.[76] the amount of 42, as judged by ^{15}N-H

coupling in deuteriochloroform at low temperatures is 2%.[76b]

Electron-withdrawing groups alpha to the aza nitrogen shift the equilibrium 41 ⇌ 42 and 43 ⇌ 44 in favour of the pyridinol tautomers.[70] Groups beta to the aza nitrogen have a smaller effect. Beak[68] has shown that in the gas phase the hydroxy tautomers 42 and 44 predominate over 41 and 43 by a ratio of 2.5:1 and > 10:1 respectively. On the other hand, in the strongly polar solvent water the pyridone tautomers 41 and 43 are favoured by a ratio of 910:1 and 1900:1 respectively.

Dubois has shown, by temperature-jump relaxation spectroscopy, that 2-pyridone in aprotic solvent interconverts between its two tautomeric forms via dimerization.[77] Water and methanol appeared to be efficient catalysts for this process.[77] Similarly, heterodimers are formed between carboxylic acids[78] and 2-pyridone which enhance the equilibrium towards the lactim in aprotic solvents. However, basic solvents and metal cations inhibit dimerization.[77]

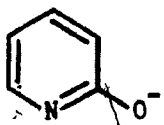
By analogy to the process put forth by Dubois, water should catalyze the equilibrium 41 ⇌ 42 as illustrated in equation II.1.



41 47a 47b 42 II.1

CNDO/2 approximations, with full geometry optimization, placed the first heterodimer 47a with lowest energy of formation for one water molecule.[80]

Protonation on the pyridones occurs on the oxygen atom as determined by NMR in concentrated D_2SO_4 for 2-pyridone.[81] The anion of 2-pyridone (48) in its ground state has the negative charge distributed mainly on the oxygen atom.[82,83b] Both 2- and 4-pyridone anions (48 and 49) respectively, behave as phenoxides in electrophilic reactions (see later).



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49

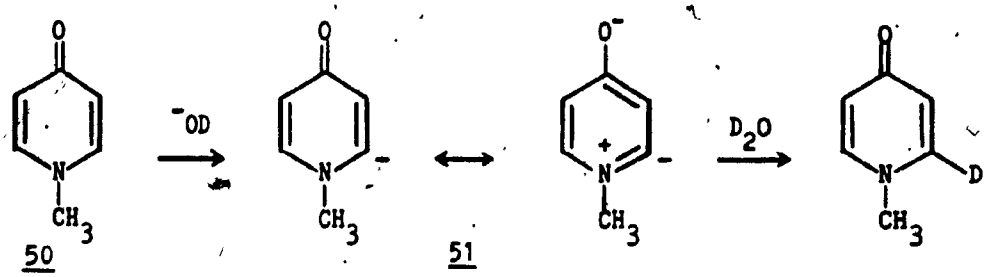
REACTIONS OF THE PYRIDONES

Hydrogen-Deuterium Exchange

Treatment of N-methyl-4-pyridone (50) and 4-methoxy-N-methylpyridinium fluoroborate with deuteriated water in base produce the respective 2,6-dideuterio compounds. In the case of 1,2,6-trimethyl-4-pyridone the 2- and 6-methyl hydrogens are exchanged.[84]

Beak[84] justified these observations as occurring via the ylide intermediate 51. A concerted protonation of the oxygen atom of the

carbonyl group may be invoked to strengthen the analogy to the relatively facile exchange of the 4-methoxy-N-methylpyridinium fluoroborate.



50 51

4-Pyridones exchange at C-3 and C-5 via their free-base as in the case of 2,6-dimethyl-4-pyridone, 4-pyridone, and 1-hydroxy-4-pyridone.[85b]

For 2-pyridone and its derivatives, exchange occurred at C-3 and C-5 apparently to the same extent.[81,85a] However, the kinetics were complicated by the unequivalence of the reactive sites and poorly separated NMR signals.[85a] This study concluded that the exchange occurred on the free-base form of the substrate.

Nitration

4-Pyridones can be mono- and di-nitrated smoothly at positions 3 and 5.[79,86] Katritzky et al. studied the nitration kinetics of 2- and 4-pyridones in acidic media.[86] Since the shape of the rate profiles for 4-pyridone, 4-methoxypyridine, and 2,4,6-trimethylpyridinium cation were all similar, they concluded that the substrates undergo nitration as their conjugate acids in 80-85% sulfuric acid. The similarity between

the actual rates for 4-pyridone and its O- and N-methyl derivatives at any one acidity and temperature provided further support for this view.

In contrast, the rate profiles of 3-nitro-4-pyridone, 3- and 5-methyl-2-pyridone, and 1,5-dimethyl-2-pyridone closely resembled each other but differed from that of the 2,4,6-trimethylpyridinium cation. This suggested that the 2-pyridones may be nitrated via the small portion of the free base. For low acidities the reaction of 4-pyridone with NO_2^+ ions proceeds by way of its free-base form.[86]

The kinetics of nitration of 2-pyridone itself have not been studied. The problem with this substrate is two-fold: to determine the reacting form and the orientation of the electrophile. On the synthetic scale, 2-pyridone is nitrated mainly at position 3 with some 3,5-dinitro-2-pyridone formed.[69] Similarly, reaction of 6-methyl-2-pyridone with nitric acid in glacial acetic acid gave the product of nitration at C-3.[69] The preferred ortho nitration is in marked contrast to the behaviour of 2-methoxypyridine which is nitrated at C-5 only,[69] suggesting that the molecule in the pyridone form which is undergoing substitution.

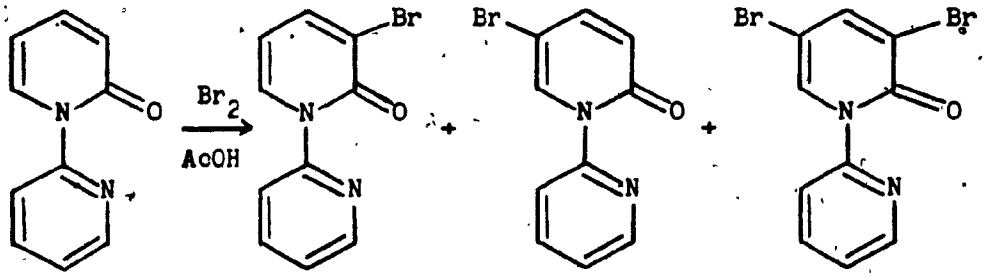
N-methyl-2-pyridone reacts similarly in 62% nitric acid in the absence of sulfuric acid to give 3-nitro and 3,5-dinitro products. By analogy to its 2-pyridone tautomer, it also reacts via its free base.

Halogenation

Direct halogenation of 2-pyridone in weakly alkaline polar solvents readily leads, as is well known, to polychloro and polybromo compounds,

while on iodination 5-iodo-2-pyridone is produced in poor yield.[154] In most cases the reaction of 2-pyridone with bromine in water or iodine in potassium carbonate solution, gave rise to the 3,5-dihalogeno-2-pyridone even under mild conditions.[69] There have been instances of monohalogenation accompanied by the formation of the 3,5-dihalo product with an apparent para directing[69] ability of the hydroxyl group.

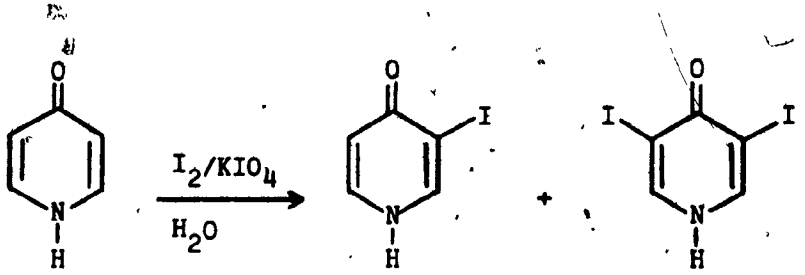
N-substituted 2-pyridones react easily with bromine. Thus, N-(2'-pyridyl)-2-pyridone has been reported to react with one equivalent of bromine to give the product ratios outlined in equation II.2, after gas chromatographic analysis of the products.[88]



II.2

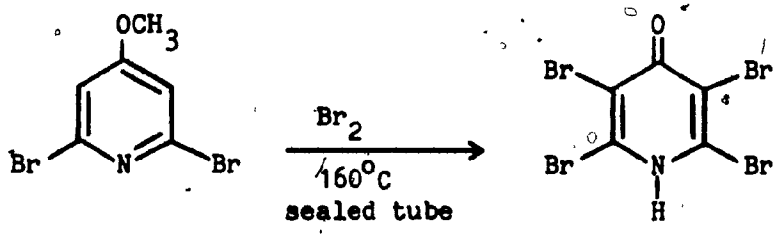
N-methyl-2-pyridone showed the same reactivity towards halogen as 2-pyridone and the reactions are summarized elsewhere.[69] As noted above, ethers of 2-pyridone are halogenated exclusively at C-5.[83,89]

4-Pyridones behave as expected and are usually dihalogenated at C-3 and C-5.[69] Iodination of 4-pyridone appears to be the only reaction reported that is controllable, to give 3-iodo-4-pyridone with the formation of appreciable amounts of the 3,5-diiodo product.[154]



43 50% 21%

Careful scrutiny of the literature revealed that 4-methoxypyridine is not brominated in aqueous solution under normal conditions. The reported bromination of 2,6-dibromo-4-methoxypyridine (51) by Hertog[90] yielded 52 after 48 hours.



51 52

Tautomeric Equilibrium Constants and UV Data

The UV spectral parameters, needed for the determination of product ratios, are listed in Table XVII. Also in this table are reported the various equilibrium constants needed for the interpretation of the kinetics and of the rate profiles. The pK_as which were not available from the literature were measured spectrophotometrically to complete the set.

After the unambigous synthesis of the 3- and 5-bromo derivatives

of 2- and 4-pyridone (and their N-methyl derivatives), product ratios were determined by comparing their NMR, UV, and IR data with those of the bromination mixtures.

Equilibrium constants are important tools in the interpretation and determination of rate profiles and rate constants. Illustrated below (Scheme IV) are four tautomeric forms of 2- and 4-pyridones capable of being brominated. The various equilibria indicated with letters are also listed in Table XVII. Such constants are an integral part of the rate law and only the right choice will enable a correct interpretation of the results. Fortunately the magnitudes of pK_as are sufficiently far apart that at a particular pH only one or two of these forms may be competing for bromine.

Scheme IV. Representation of Equilibria for 2- and 4-Pyridones.

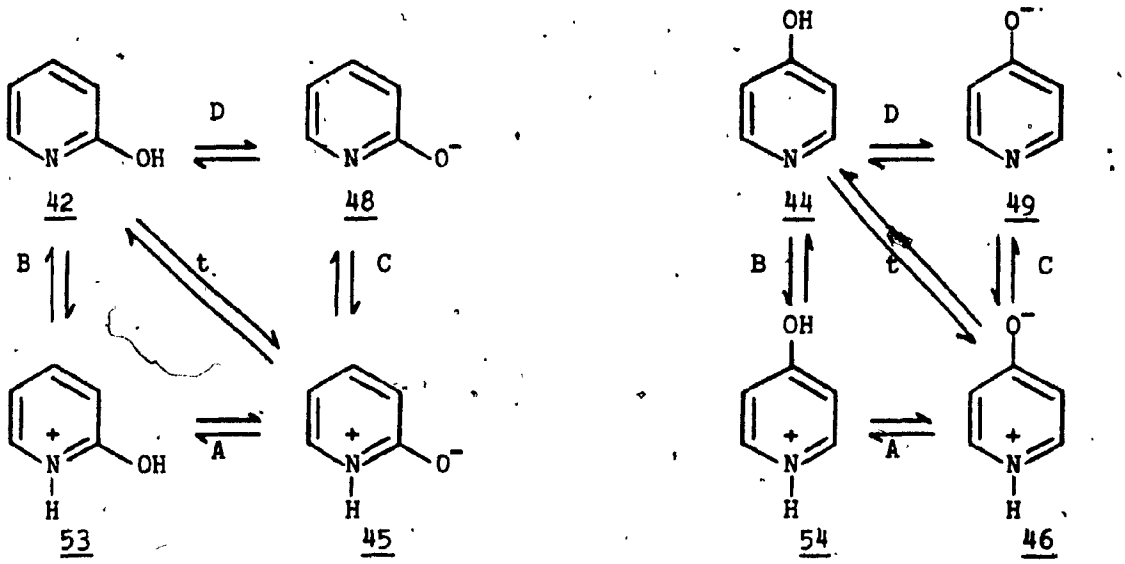


Table XVII. UV Spectral Parameters and pK_as for the Pyridones and 2- and 4-Methyl Ethers.

Compound (References)	pK	pH or H_o	λ_{max} in nm (log ϵ)[a]
2-Pyridone	A^b = 0.75[c]	-4.9	209(3.51), 277(3.82)
(20b,28,29,83b)	B^b = 3.71[c]	0.77[d]	<225(>3.34), 281(3.74)[d,e]
	C^b = 11.62[c]	7.68	226(3.37), 294(3.79)[e]
	D^b = 8.66[c]	-[f]	288(4.00), 292(4.00)
	t^b = -2.96[c]	-[i]	230(3.95), 298(3.66)
1-Methyl-2-pyridone	0.32[b]	0.77[d]	<225(>3.54), 288(3.69)[d,e]
(20b,28)		5	226(3.78), 297(3.76)
		7.68	227(3.42), 297(3.72)
2-Methoxypyridine	3.28	-3.6	279(3.85)
(20b,28,83b)		7	269(3.51)
3-Bromo-2-pyridone	-2.15	-7.0	226(3.47), 290(3.90)
(83)	10.42	0.77[d]	231(3.59), 306(3.85)[d,e]
		7.68	230(3.61), 306(3.89)[e]
		-[g]	231(3.93), 303(3.81)
5-Bromo-2-pyridone	-0.06	-3.6	225(3.86), 296(3.75)
(83)	10.03	0.77[d]	231(3.94), 306(3.69)[d,e]
		7.68	232(3.91), 310(3.65)[e]
		-[h]	237(4.09), 306(3.62)
1-Methyl-3-bromo-	-2.2[j]	0.77[d]	232(3.57), 308(3.85)[d,e]
2-pyridone		7.68	231(3.57), 309(3.89)[e]
1-Methyl-5-bromo-	-0.1[j]	0.77[d]	233(3.91), 311(3.64)[d,e]
2-pyridone (83a)		H_2O	235(3.91), 313(3.65)
		7.68	233(3.90), 313(3.64)[e]

Table XVII. Continued.

Compound (References)	pK	pH or H_0	λ_{max} in nm (log ϵ)[a]
3,5-Dibromo-2-pyridone (83)	-2.45	-7.0	216(4.23), 235(3.78), 313(3.79)
	8.43	0.77[d]	232(3.81), 322(3.81)[d,e]
		7.68	235(3.86), 321(3.84)[e]
		-[h]	240(3.96), 318(3.64)
1-Methyl-3,5-dibromo-2-pyridone	-2.5[j]	0.77[d]	236(3.80), 324(3.84)[d,e]
		7.68	236(3.74), 324(3.78)[e]
3-Bromo-2-methoxypyridine (83)	-[k]	5	220(3.78), 280(3.71)
5-Bromo-2-methoxypyridine (83)	1.14	-3.6	225(3.93), 300(3.78)
		5	222(4.01), 284(3.54)
3,5-diBromo-2-methoxypyridine (83b)	-1.50	-3.6	217(4.19), 236(3.75), 305(3.83)
4-Pyridone (29,91)	A^b = 3.27[c]	1.0	234(3.96)
	B^b = 6.56[c]	13.4	239(4.12)
	C^b = 11.09[c]		
	D^b = 7.80[c]		
	t^b = -3.29[c]		
1-Methyl-4-pyridone (28)	3.33		
4-Methoxypyridine (29,91)	6.62	4.0	236(4.04)
		9.0	218(3.91)
3-Bromo-4-pyridone	1.37[l]	0.70[l]	243(3.71), 263(3.57)[l]
	9.46[m]	7.02	262(4.06)[e]
		-[g]	243(3.94), 271(3.76)[e]

Table XVII. Continued.

Compound (References)	pK	pH or H_o	λ_{max} in nm (log ϵ)[a]
1-Methyl-3-bromo-4-pyridone	1.52[l]	0.96[l]	248(3.74), <u>270(3.67)</u>[e,l]
		2.43	270(4.04)[e]

[a] Underlining indicates a shoulder or inflection.
[b] At 20°C.
[c] Refers to equilibrium in Scheme IV.
[d] pH = p[HBr] (titration). No KBr was added to the solution.
[e] This work: [KBr] = 1.00 M (unless otherwise noted) and at 25°C.
[f] [NaOH] = 1.00 M, [g] 0.100 M, [h] 0.010 M.
[i] Solvent was cyclohexane.
[j] Assumed.
[k] Hydrolysis was too rapid.
[l] $[HClO_4] + [NaClO_4] = 0.150$ M at 25°C.
[m] [KBr] = 0.100 M at 25°C.

The Rate Law

All the pyridones studied in this chapter, were easily brominated in 1.00 M aqueous KBr to give mono and disubstituted products. The general equation II.3 describes the reaction, where PHO is the pyridone substrate.

$$PHO + Br_2 \xrightarrow[H_2O]{KBr} \text{products} \qquad \text{II.3}$$

The rate of disappearance of the tribromide band (λ_{max} = 267 nm) was

followed in double-beam experiments, where the reference wavelength was set at 340 nm. Assuming negligible tribromide ion reaction, the more general rate law for the bromination of the parent compounds 41 and 43 is given by equation II.4 (structures are depicted in Scheme IV).

$$\text{rate} = (k_z[P^+HO^-] + k_3[P^+HOH] + k_h[POH] + k_2[PO^-])[Br_2] \qquad \text{II.4}$$

In this equation P^+HO^- is the zwitterionic form (i.e. 45 or 46) P^+HOH is the protonated form (53 or 54), POH is the hydroxy form (42 or 44), and PO^- is the anion (48 or 49). With the exception of the equilibrium defined by t, all equilibria are pH dependent and as such the terms in equation II.4 will vanish at different pH.

Combining the pH dependent forms:

$$\text{rate} = (k_1[PHO] + k_2[PO^-] + k_3[P^+HOH])[Br_2] \qquad \text{II.5}$$

where PHO (defined in II.3) is either 41 or 43. Substituting the appropriate equilibrium constants, the rate law in terms of [PHO] and $[Br_2]$ is given by:

$$\text{rate} = (k_1 + k_2K_C/[H^+] + k_3[H^+]/K_A)[PHO][Br_2] \qquad \text{II.6}$$

Substituting for stoichiometric concentrations, equation II.6 becomes:

$$\text{rate} = \frac{(k_1 + k_2K_C/[H^+] + k_3[H^+]/K_A)}{(1 + K_C/[H^+] + [H^+]/K_A)} ([PHO]_o - [Br_2]_o + [Br_2])[Br_2] \qquad \text{II.7}$$

This second-order equation can be analyzed as outlined in the Experimental for equation V.2 (page 212) for $[P]_o > [Br_2]_o$. The first-order rate constant is given by:

$$k_1^{obsd} = \frac{(k_1 + k_2K_C/[H^+] + k_3[H^+]/K_A)([PHO]_o - [Br_2]_o)}{(1 + K_C/[H^+] + [H^+]/K_A)} \qquad \text{II.8}$$

The second-order rate constant is given by:

$$k_2^{obsd} = \frac{k_1^{obsd}}{([PHO]_o - [Br_2]_o)} \qquad \text{II.9}$$

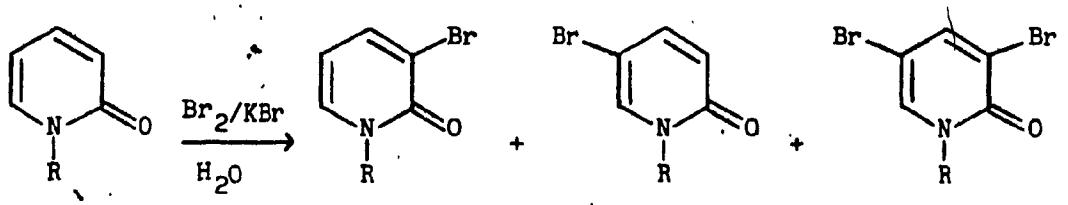
for the process in equation II.3.

2-PYRIDONE AND DERIVATIVES

Product Study

Product analysis was conducted via UV (see Table XVIII) and NMR spectroscopies. Attempted gas chromatographic study was unsuccessful due to lack of elution of the silylated products (cf. GC study for phenols) and was not pursued further.

UV spectra of 1:1 mixtures of bromine and 2-pyridone at pH 0.77 (this is p[HBr]) yielded a broad band at 304 nm (log ϵ = 3.72) whose extinction coefficient was less than that of 3-bromo-2-pyridone (log ϵ = 3.81 see Table XVIII and compare value with Table XVII). The maximum absorption wavelength was situated somewhere between that for 3-bromo and 5-bromo derivative. Since the extinction coefficient for the 5-bromo derivative is about one half of that for 3-bromo, it was qualitatively deduced that more 3-bromo-2-pyridone formed compared to 5-bromo-2-pyridone.



55 56 57 58

a R = H; b R = CH_3

The N-methyl derivative 55b after a 1:1 molar mixture with bromine

in water, produced a UV spectrum λ_{max} = 308 nm, log ϵ = 3.74. The appearance of the spectrum and extinction coefficient at the maximum, pointed to the 3-bromo isomer 56b as being the major product. From the broadness of the band, it was impossible to exclude 57b, 58b, or even some residual 55b as components of the mixture. In acidic buffer there was a preference for the 3-bromo product in the aqueous bromination of 2- and 1-methyl-2-pyridone.

In basic medium pH 7.68, 2-pyridone and bromine mixed in a 1:1 molar ratio in 1.00 M KBr produced a band λ_{max} = 302 nm log ϵ = 3.71. This band was shifted towards the visible relative to bromination mixture in acid, pointing to dibromination. The lower extinction coefficient was perhaps suggestive that more 5-bromo-2-pyridone (67a) be produced initially. In fact, by analyzing the absorbance changes at several wavelengths, using the mass balance and extinction coefficients of 2-pyridone 55a and the bromo derivatives: 3-bromo 56a, 5-bromo 57a, and 3,5-dibromo 58a the ratio [57a]/[56a] ≃ 4.4. Since 5-bromo-2-pyridone 57a is twice as reactive as 3-bromo-2-pyridone 56a at pH 7.68, this value probably represents a lower limit for the isomer ratio 57a:56a at pH 7.68.

Table XVIII. UV Parameters of Mixtures of 2-Pyridones after Bromination.

Compound ($[Sub]_o$)	$\frac{[Sub]_o}{[Br_2]_o}$	pH	λ_{max} in nm (log ϵ)[a]
2-Pyridone	0.667	0.77[b]	231(3.87), 309(3.70)
(2.00×10^{-4} M)	1.000		229(3.79), 304(3.72)
	2.000		227(3.65), 286(3.68), 304(3.62)
	0.667	7.68[c]	232(3.73), 313(3.72), 325(3.60)
	1.000		229(3.65), 302(3.71), 325(3.49)
	2.000		228(3.56), 297(3.75)
1-Methyl-2-pyridone	0.667	0.77[b]	233(3.85), 312(3.73)
(2.00×10^{-4} M)	1.000		231(3.80), 308(3.74)
	2.000		227(3.68), 299(3.69)
	0.667	7.68[c]	232(3.50), 311(3.25)
	1.000		231(3.51), 307(3.45)
	2.000		229(>3.47), 298(3.64)

[a] Refers to concentration of product mixture which was always 2.00×10^{-4} M. Underlined results indicate shoulder or inflection.

[b] pH = p[HBr], no added KBr.

[c] Universal buffer was used with a constant ionic strength 0.10 M and [KBr] = 1.00 M.

The NMR data for 2-pyridones and derivatives are collected in Table XIX. For 2-pyridone the NMR spectrum taken after a 3:2 ratio of substrate and bromine were mixed, clearly showed the presence of 3-bromo-2-pyridone 56a. The H-5 signal, a triplet, assignable to 56a was well separated; however, the H-3 signal was covered by those of 2-pyridone itself and other products using the Varian A-60 spectrometer.

NMR spectroscopy proved more useful in discerning orientation in the case of bromination of the N-methyl derivative. The isomeric bromopyridones 3-bromo 56b and 5-bromo 57b were easily distinguished, even in mixtures of the two. After about one equivalent of bromine was added, the ratio of [56b]/[57b] was found to be 7:2 by integration of signal intensities of H-5 and H-4 respectively. Moreover, the less soluble dibromo compound 58b was seen as a precipitate in the NMR tube.

Table XIX. NMR Parameters[a] of Substituted Pyridines.

Substituents on Pyridine (Medium)	Chemical Shifts (δ) 3-H	4-H	5-H	6-H	CH_3	Coupling Constants (Hz)
2-OH[74a]	7.3	8.2	7.3	8.2	-	$J_{3,4} = J_{4,5} = 6.5$ $J_{5,6} = 6.5$, $J_{4,6} = 2.5$
3-Br-2-OH (D2O)	--	7.73	6.56	8.20	--	$J_{4,5} = J_{5,6} = 7.0$ $J_{4,6} = 2.0$
5-Br-2-ONa (D2O)	6.45	7.67	--	8.06	--	$J_{3,4} = 10$, $J_{4,6} = 2.5$
3,5-diBr-2-OH (D_2O/NaOD)	--	7.82	--	7.82	--	
1-Me-2-O[2]	6.57	7.26	6.15	7.31	3.59	
1-Me-2-Br-2-O (D2O)	--	6.64	8.12	8.12	3.86	$J_{4,5} = J_{5,6} = 7$ $J_{4,6} = 2$
1-Me-5-Br-2-O (D_2O)	7.75	6.60	--	7.98	3.61	$J_{3,4} = 10$, $J_{4,6} = 3$
2-OMe (Neat/TMS)	7.20	7.94	7.20	8.71	4.26	$J_{5,6} = J_{4,5} = 6.0$ $J_{4,6} = 2.7$
1-Me-3,5-diBr-2-O (c. DCl)[b]	--	~9.4	--	~9.4	~4.3	
5-Br-2-OMe[c]	6.87	7.88	--	8.60	4.04	$J_{3,4} = 9$, $J_{4,6} = 2.7$

[a] From this work unless otherwise specified. The standard reference in D_2O was DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate).

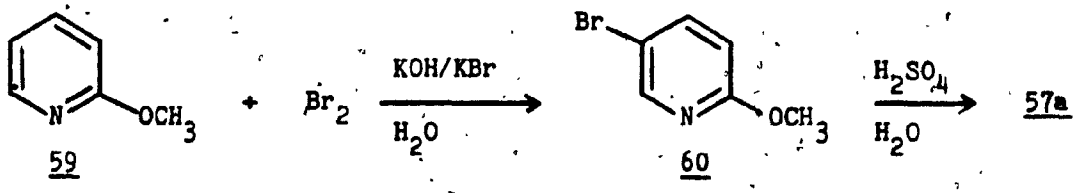
[b] No standard was added.

[c] Neat bromination mixture. Reference was TMS.

On a synthetic scale, the reaction of equimolar quantities of 2-pyridone and bromine in acetic acid yielded 85% (based on bromine) of 3,5-dibromo-2-pyridone (58a). The same reaction in water containing one equivalent of KOH also produced 58a in the same yield. However, when the medium used was 1.00 M aqueous KBr, a 78% yield of 3-bromo-2-pyridone (56a) was obtained. This material had identical NMR and IR spectra to those of 56a made by the literature procedure. Also methylation gave 56b identical to that prepared by other routes.

Bromination of 1-methyl-2-pyridone (55b) in aqueous perchloric acid gave its 3,5-dibromo derivative 58b, which crystallized from solution in 67% yield, and unreacted starting material.

A synthetic reaction of equimolar amounts of bromine and 2-methoxypyridine (59) in 1.00 M aqueous KBr containing 0.5 equivalents of KOH, gave after work-up a 63% yield of 5-bromo-2-methoxypyridine (60). It is not to be implied from the yield that the remaining products are those of dibromination. The reaction is slow with possible loss of bromine or incomplete bromination. In fact, the NMR spectrum of the product mixture, after extracting with chloroform, indicated 60 and starting material 59. Compound 60 had been previously synthesized in acetic acid containing sodium acetate.[83] The reaction in water was to confirm that no change in orientation of the bromine molecule occurred upon changing solvent. Compound 60 was further identified by its hydrolysis in 4 M aqueous sulfuric acid to 57a.



It should be stressed, as a final point, that in none of the spectral studies (NMR or UV) was there any evidence of intermediate of significant lifetime between the substrates and their brominated products.

Kinetic Studies

The rates of reaction of 55, 56, 57, and 59 with bromine in aqueous media in the range $0 < pH < 8$, were measured by the stopped-flow method. In the presence of a large excess of substrate, bromine disappearance was first-order and the pseudo-first-order rate constants (k_1^{obsd}) increased linearly with the substrate concentration (see Table XX and Figure 21).

Second-order rate constants k_2^{obsd} were obtained from k_1^{obsd} by dividing by the difference in concentration of reactants and multiplying by the correction factor for free bromine at different pH (equation I.21). In some instances, for example when $[PHO]_o < 5[Br_2]_o$, absorbance data were analyzed directly for second-order behaviour. In such cases, no value of k_1^{obsd} is given in Table XX. However, the reported values of k_2^{obsd} have been corrected for the fraction of free bromine. They were invariant with both substrate and bromine concentrations. Moreover, the values of k_2^{obsd} obtained from both approaches agreed well. Thus, at any given pH the reaction of bromine with the substrates follows a second-order rate law.

Table XX. First- and Second-Order Rate Constants for the Bromination of 2-Pyridone and Derivatives.[a]

pH	$[PHO]_o \times 10^6$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	$k_2^{obsd} \times 10^{-3}$ $M^{-1}\ sec^{-1}$
2-Pyridone[b]				
-0.07[c]	1529	500	—	2.33
1.01[d]	764.7	1000	—	11.5
	764.7	500	—	11.5
	1529	500	—	11.5
1.78	1000	500	1.04	18.6
2.47	764.7	500	—	21.1
3.25	1000	500	1.24	22.1
3.53	1529	500	—	22.6
	764.7	500	—	22.7
4.05	1000	500	1.28	22.9
4.53	382.3	100	—	24.1
	382.3	500	—	23.2
	382.3	1000	—	22.7
5.53	382.3	500	—	25.0
6.47	764.7	1000	—	40.7
6.92	382.3	150	—	104
7.66	1000	500	18.2	335
7.74	764.7	500	—	828
1-Methyl-2-pyridone[e]				
-0.07[c]	500	500	0.242	9.14
	1000	100	0.505	9.13
1.02[d]	500	100	0.980	37.0
	1000	100	2.04	36.5
2.24	500	450	1.41	52.6
2.98	500	100	1.40	48.5
	500	500	1.44	54.3
39.2	500	100	1.41	48.9

Table XX. Continued

pH	$[PHO]_o \times 10^6$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	$k_2^{obsd} \times 10^{-3}$ $M^{-1}\ sec^{-1}$
1-Methyl-2-pyridone[e]				
3.93	4000[f]	500	9.17	39.5
4.37	1000[f]	500	2.45	43.8
4.52	1000[f]	100	2.78	47.8
4.95	500	100	1.39	48.2
4.99	500[f]	100	1.38	47.9
5.98	500	100	1.48	51.3
6.02	200[f]	100	0.531	47.4
6.93	500	250	1.06	38.3
3-Bromo-2-pyridone				
-0.07[c]	2000	500	0.184	1.60
0.11[g]	2000	500	0.174	1.52
1.05[h]	1000	250	0.0913	1.59
2.07	2000	500	0.201	1.75
2.73	2000	500	0.207	1.80
3.96	1000	500	0.122	2.18
	2000	500	0.239	2.09
4.91	2000	500	0.522	4.55
5.51	1000	250	0.660	11.5
	2000	250	1.26	11.0
6.23	800	500	1.85	42.0
6.29	2000	500	5.90	51.5
6.66	1000	500	6.28	112
7.36	250	250	5.39	413
3-Bromo-1-methyl-2-pyridone				
0.11[g]	1000	250	0.151	2.63
1.05[h]	800	250	0.123	2.71
2.64	500	250	0.0745	2.67
	1000	250	0.152	2.66

Table XX. Continued

pH	$[PHO]_o \times 10^6$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	$k_2^{obsd} \times 10^{-3}$ $M^{-1}\ sec^{-1}$
3-Bromo-1-methyl-2-pyridone				
4.07	500	250	0.0803	2.87
	1000	250	0.158	2.76
5.49	400	250	0.0616	2.79
	800	250	0.126	2.77
6.07	1500	250	0.235	2.71
7.47	2000	250	0.242	2.12
5-Bromo-2-pyridone[b]				
-0.07[c]	1689	500	0.0153	0.159
1.00[d]	1689	500	0.0309	0.321
2.08	422.3	500	0.0111	0.505
	844.7	500	0.0203	0.434
3.32	844.7	500	0.0243	0.519
	1689	500	0.0458	0.475
4.25	422.3	500	0.0194	0.887
5.04	422.3	100	0.127	5.23
6.15	211.2	100	0.600	50.7
	295.6	100	0.810	48.1
	422.3	100	1.27	52.4
7.12	422.3	500	16.8	76.8
	844.7	500	33.4	71.4
8.18	168.9	500	45.9	656
5-Bromo-1-methyl-2-pyridone				
-0.07[c]	2000	500	0.0505	0.441
1.00[d]	2000	500	0.0809	0.706
2.22	2000	500	0.0870	0.757

Table XX. Continued

pH	$[PHO]_o \times 10^6$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	$k_2^{obsd} \times 10^{-3}$ $M^{-1}\ sec^{-1}$
5-Bromo-1-methyl-2-pyridone				
2.99	1000	500	0.0394	0.706
	2000	500	0.0834	0.727
	3000	500	0.127	0.729
3.91	2000	500	0.0791	0.690
5.04	2000	500	0.0988	0.862
6.98	975	250	0.0472	0.844
7.93	1950	250	0.0887	0.784
2-Methoxypyridine[f]				
2.01	25000	1000	0.00154	0.00105
3.10	40000	500	0.0126	0.00538
3.82	20000	500	0.00827	0.00704
3.96	6000	500	0.00240	0.00687
	12000	500	0.00508	0.00724
4.03	16000	500	0.00760	0.00809
5.73	20000	1000	0.0116	0.00995
6.56	6000	500	0.00312	0.00891
	12000	500	0.00592	0.00875
8.21	12000	1000	0.00786	0.0111

[a] Each datum is the average of three or more runs with a correlation coefficient better than 0.9995. Concentration of KBr was 1.00 M and ionic strength of the buffer was 0.01 M, unless otherwise specified. Temperature was 25°C.

[b] Numbers with non-zero digits signify that the sodium salt was used in the run. This compound was assumed to be the dihydrate.

[c] H_o value for 1.38 N H_2SO_4.

[d] [HBr] = 0.10 M, [KBr] = 0.90 M.

[e] Unless otherwise noted, the substrate was used as its hydrobromide salt.

[f] The substrate was used as received from Aldrich.

[g] The H_o value for 1.00 N H_2SO_4.

[h] Sulfuric acid was used to adjust the pH in a 1.00 M KBr medium.

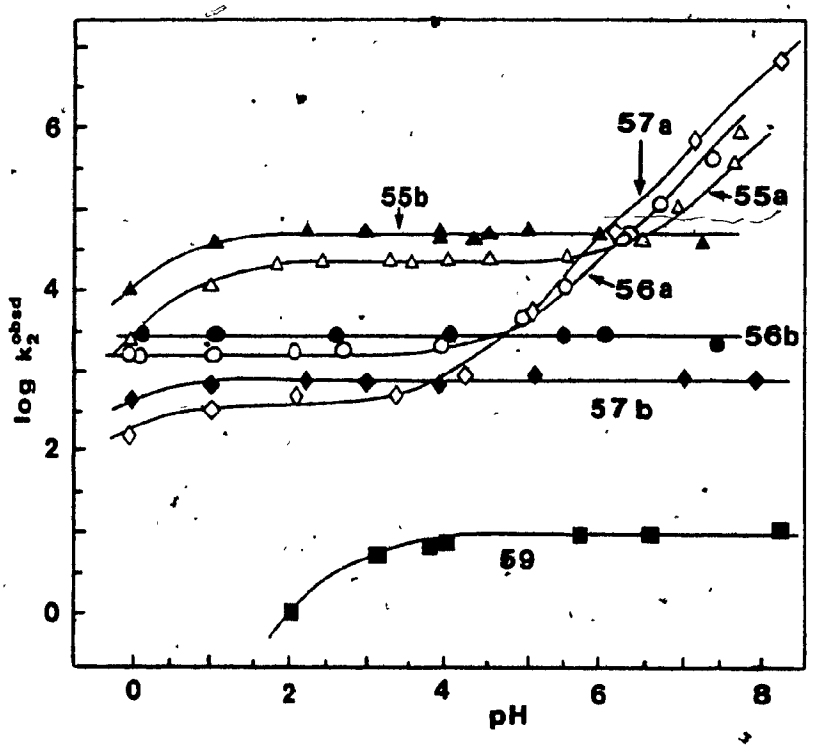


Figure 21. Rate profiles for the bromination of 1-methyl-2-pyridone (55b, ▲), 2-pyridone (55a, Δ), 1-methyl-3-bromo-2-pyridone (56b, ●), 3-bromo-2-pyridone (56a, O), 1-methyl-5-bromo-2-pyridone (57b, ◆), 5-bromo-2-pyridone (57a, ◇), and 2-methoxypyridine (59, ■) at 25°C and 1.00 M KBr. (Numerical constants are listed in Table XX).

The variations of k_2^{obsd} for 2-pyridone 55a depicted in Figure 21, demonstrate that for high $[H^+]$ the rate is linearly dependent on the pH with curvature around the protonation pK_A value. The terms due to the anion in equation II.8 vanish at high acidity and so k_2^{obsd} has the form:

$$k_2^{obsd} = \frac{k_1K_A + k_3[H^+]}{(K_A + [H^+])} \qquad \text{II.10}$$

The decrease in value for the rate from pH 1 to pH 0, indicates that the term $k_3[H^+]$ is much smaller than k_1K_A, and that no apparent reaction occurs the protonated form of the substrate 53. Equation II.10 can thus be simplified to:

$$k_2^{obsd} = \frac{K_A k_1}{(K_A + [H^+])} \qquad \text{II.11}$$

Around the protonation pK_A of 2-pyridone, the rate profile should curve and level to a constant value as the pH increases, since then $K_A >> [H^+]$. In this case $k_2^{obsd} = k_1$, for $k_2K_C/[H^+]$ still negligible with respect to k_1.

The behaviour outlined above is general for all the 2-pyridone derivatives. Where these have no ionizeable hydrogen, K_C is non-existent (i.e. zero) and the rate profile maintains a slope of zero for $[H^+] << K_A$.

2-Methoxypyridine (59) having its pK_A value well into the pH region, shows this behaviour most clearly. A linear variation of unit slope is shown in the range $1.5 < pH < 2$, which excludes bromination via the protonated form of the substrate.

At higher pHs ($pH > 6$) 2-pyridone (55a) and its bromo derivatives (56a, 57a) show a linearly increasing rate of reaction for decreasing acidity pointing to reaction via their anions (61 and 62). The term $[H^+]/K_A$ is very small in comparison to $K_C/[H^+]$ and thus k_2^{obsd} has the form:

$$k_2^{obsd} = \frac{k_1[H^+] + k_2K_C}{([H^+] + K_C)} \qquad \text{II.12}$$

where K_C refers to the deprotonation constant. 2-Pyridone has the highest deprotonation pK of all substrates studied. This translates into a more uncertain determination of k_2, because in terms of equation II.12: $k_1[H^+]$ and k_2K_C are comparable in the region $6 < pH < 8$. The bromo derivatives in the same pH region, show linear dependence with unit slope, indicating that $k_1[H^+] \ll k_2K_C$ and that $[H^+] \gg K_C$. Thus, k_2^{obsd} can be expressed, in this context, as:

$$k_2^{obsd} = k_2K_C/[H^+] \qquad \text{II.13}$$

In Table XXI are collected the constants for the reaction of bromine with 2-pyridones in aqueous solution outlined in equations II.11 and II.12. The curves in Figure 21, drawn through the data points, were calculated using equations II.10 and II.11, and the parameters given in this table.

Table XXI. Summary of Constants for the Reaction of Bromine with 2-Pyridone Derivatives in Aqueous Solution.[a]

Substrate	$(pK_A)^b$	$(pK_C)^b$	k_1 $M^{-1}sec^{-1}$	k_2K_C X 10^3 sec^{-1}	k_2 X 10^{-8} M^{-1} sec^{-1}
2-Pyridone	0.86	11.62	22000	7.2	30
1-Me-___	0.56		47000		
3-Br-___	-2.15	10.42	1650	23	6.0
1-Me-3-Br-___	-2.2		2720		
5-Br-___	-0.06	10.03	380	46	4.9
1-Me-5-Br-___	-0.1		760		
2-Methoxypyridine	2.92		9.5		

[a] Parameters used to generate profiles in Figure 21 with equations II.11 and II.12.

[b] Taken from Table XVII.

In summary, the reaction of bromine with all of the substrates followed a second-order rate law for constant pH. Second-order rate constants vary with pH in a manner consistent with reaction upon the free-base form of the substrate. But, the pyridones bearing an ionizeable hydrogen, also react via their respective anions at higher pH.

Competitive Consecutive Process and Second-Order Kinetics

Not all has been said for the bromination rates of 2-pyridone vis-a-vis dibromination. It was alluded to above, when discussing UV products, that there appeared to be a change in orientation of the halogen at pH 7.68, causing a higher 5-bromo-to-3-bromo product ratio. However, dibromination occurs to an unknown extent.

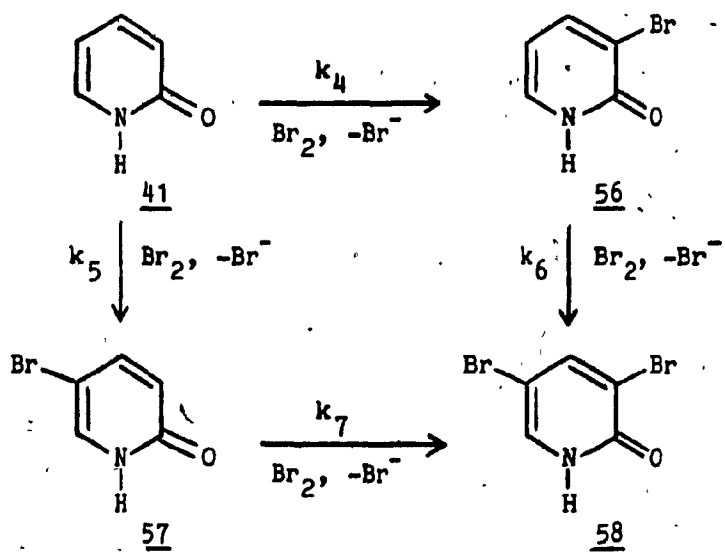
It is puzzling how lightly the literature seems to deal with this problem. For instance, Bell[53] had to correct for the dibromination of phenol up to 15%; however, both the methodology and correction factor are obscure. At this time the author was unaware of the works of Frost[100] and Svirbely[101] The former handled the problem of multiple reactivity graphically by analyzing product ratios at various times during the reaction. The latter used an iterative computer program, based upon the steady state approximation, to calculate individual rate constants. Frost and Svirbely imposed, for convenience, the initial condition $2A_o = B_o$ (stoichiometric amounts) for the two reactants. Both of these techniques were impractical, since no product ratio is determinable from stopped-flow results. In fact, inherent in their

calculations is the assumption that it is the kinetics of formation of products which is followed.

The search for a solution of competitive second-order reactions was begun and accomplished (see Appendix). The main reason was to determine how bromine or tribromide ion disappearance would be affected and appear in the UV traces. This evolved into an easy solution that for equivalent amounts of substrate and bromine, the decay should be second-order as in monobromination reaction where the reactants are mixed in stoichiometric amounts.

These conditions and calculations proved more elegant than at first anticipated. Similar kinetics done on 4-pyridone and phenols will show further the general applicability of the mathematics. Although unable to determine the individual reaction constants k_4 and k_5, depicted in Scheme V, k_6 and k_7 were readily determinable from the monobromination of 3- and 5-bromo-2-pyridone (see Table XXI).

Scheme V. Parallel Consecutive Bromination of 2-Pyridone.



There are advantages to this method. Firstly, the need for lower amounts of substrate (2-pyridone) enabled the kinetic study at higher pH because of a decreased rate. Secondly, any impurity present in the substrate would not alter the bromination constant from its actual value. If this impurity is faster reacting there would be no problem because the slower rate-determining process would be analyzed. If the impurity is reacting slower than the substrate then the uncertainty in determining an infinity value for the absorbance would be at par with the amount of impurity brominated. Thirdly, second-order conditions would allow for any trapping of reactive intermediate by a second molecule of bromine: an otherwise undetectable process under pseudo-first-order conditions.

2-Pyridone was submitted to these second-order conditions and the traces, showing second-order decay, were analyzed as for monobromination where bromine and reactants are in stoichiometric amounts. This was done to lend support to the differential equations and ideas developed in the Appendix. Moreover, the sodium salt of 2-pyridone showed anomalous kinetic behaviour at high pH (6-7). This salt was hydrated but NMR and microanalyses showed different water content.

The constants from such second-order (one-to-one analysis) are listed in Table XXII and plotted in Figure 22. As expected, because 2-pyridone anion (48) is the slower reacting species in Figure 21 in the region $6 < pH < 8$, there is a competitive consecutive second-order process. This behaviour also explains the factor of two decrease found in k_2^{obsd} relative to the one extracted from k_1^{obsd}, if a steady state is assumed on all intermediates (see Appendix).

Table XXII. Rate Constants for the Dibromination of 2-Pyridone.[a]

pH	$[2\text{-Pyridone}]_o \times 10^7$ M	$[Br_2]_o \times 10^7$ M	$(k_2^{obsd})^b$ $M^{-1}\ sec^{-1}$
2.71	250	500	2.20×10^4
3.79	250	500	2.14×10^4
6.28	250	500	2.65×10^4
7.13	250	500	7.58×10^4
7.71	250	500	1.59×10^5
8.08	250	500	4.11×10^5
8.58	250	500	1.53×10^6

[a] Solutions were 1.00 M in KBr at 25.0°C.

[b] Data analyzed as second-order of the type A = B = $[Br_2]_o$. Correlation coefficients are all > 0.9995. Each value is the average of at least three runs and is corrected for the fraction of free bromine (equation I.21).

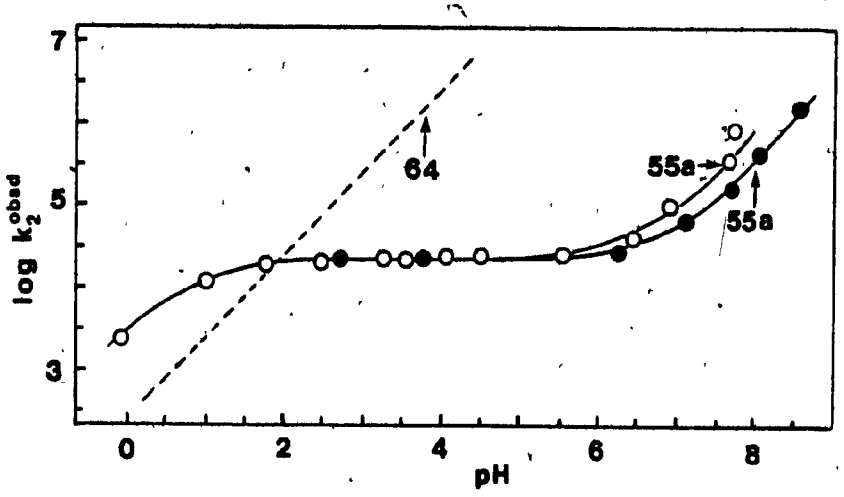


Figure 22. Rate profiles for the bromination of 2-pyridone (55a) under pseudo-first-order O and second-order ● conditions, and 3-bromo-2-hydroxypyridine (64, dotted line).

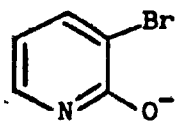
The rate constants below pH 6 are unexplicable by reaction of bromine on the lactam tautomer of 3-bromo-2-pyridone (56a), because it suggests that bromination of 2-pyridone at these pHs is the slow step of the reaction. This problem is discussed later in the next section.

Reactive Forms

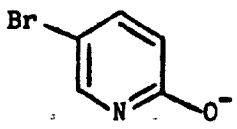
As is clearly seen in Figure 21 and from the relevant values of k_2^{obsd} in Table XXI, the tautomeric system 41 ⇌ 42 shows a reactivity towards bromine which is very similar to that shown by 1-methyl-2-pyridone (55b), but much greater (2300 X) than 2-methoxypyridine. Since the pyridone tautomer 41 predominates in aqueous solution,[20b,66,67,75,79b] this observation is compelling evidence that the lactam form is the reactive species at pH < 6. At pH > 6 reaction apparently goes via the anion 48, judging by the rate profile (Figure 21).

Similar arguments point to the lactam tautomers 56a and 57a as the reactive forms of 3-bromo and 5-bromo-2-pyridone, respectively, at pH < 4.

For pH > 4 the linear increase of log k_2^{obsd} with pH suggests that the bromo isomers also react via their anions 61 and 62.



61



62

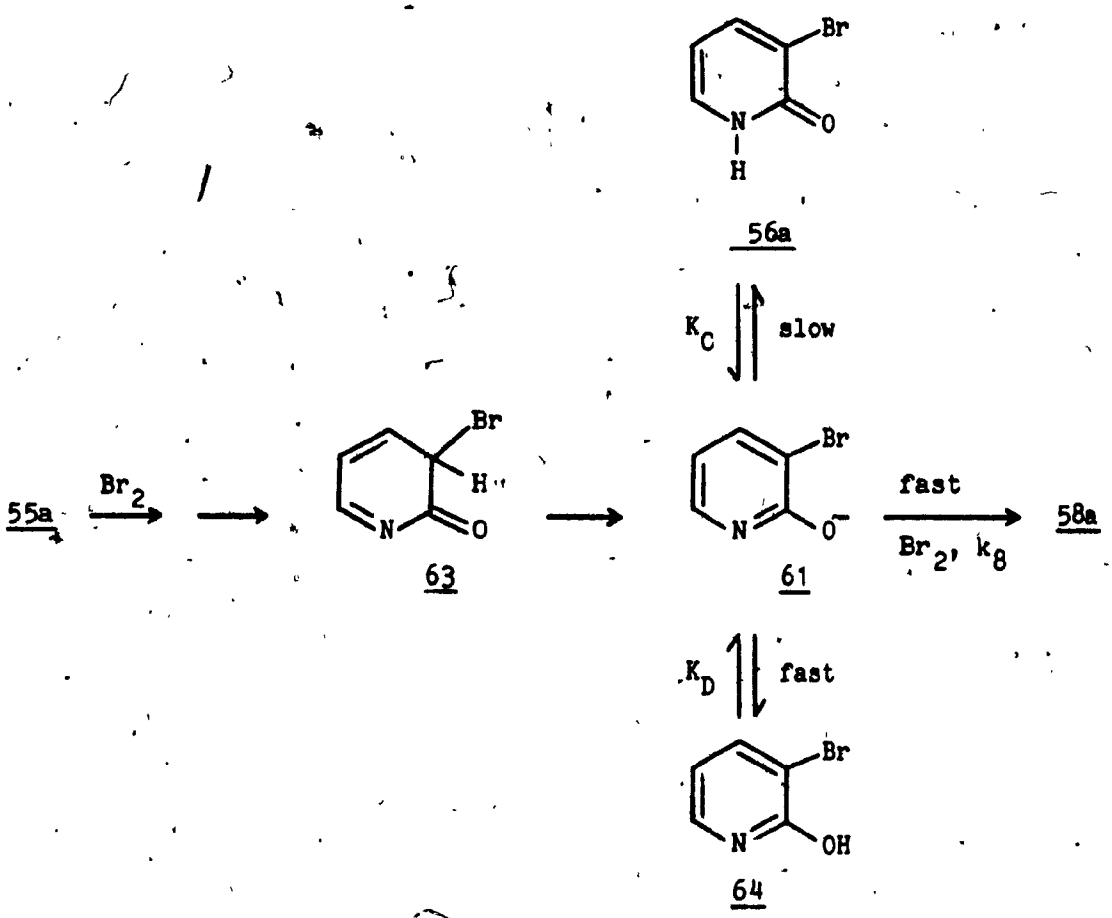
The positional selectivities observed for 55a, 55b, and 59 also show significant differences. Both 1-methyl (55b) and 2-pyridone (55a) are mainly brominated at C-3, whereas 2-methoxypyridine (59) reacts at C-5. This provides further evidence that the reactive form of 2-pyridone is the lactam 55a. In contrast at higher pH, where 2-pyridone reacts via the anion, UV spectral studies (vide supra) suggest that attack at C-5 of the anion predominates. This behaviour is reminiscent of phenols and phenoxide ions which show greater para than ortho reactivity.[53]

Katritzky and co-workers[84,85] studied the nitration of 2-pyridones in strong acid and their hydrogen isotope exchange in deuteriated acid at elevated temperatures. For these reactions they also concluded that the reacting species was the free base form of the tautomer 55a.[84,85]

The bromination results above obtained under pseudo-first-order conditions are easily explained by the reactivity of the lactam forms of the pyridones, and, where applicable, their anions. The discussion below addresses the problem of results obtained under second-order conditions in the dibromination of 2-pyridone in the pH range 2-6.

In order to explain the values of the rate constants in Table XXII (Figure 22) at pH < 6, consider that 3-bromo-2-pyridone, the major product of monobromination (the explanation for the 5-bromo-2-pyridone would be similar), reacts exclusively via its anion derivative 61 when 2-pyridone is dibrominated.

Scheme VI. Pathways for Dibromination of 2-Pyridone.



By analogy with 2-pyridone (see Scheme IV), where pK_D = 8.66 for 42 ⇌ 48 and pK_C = 11.62 for 45 ⇌ 48 (Table XVII), it can be assumed that the difference $pK_C - pK_D = 3$ for 56a ⇌ 64 (i.e. of the same order of magnitude as that for 2-pyridone). This would mean that pK_D for 64 ⇌ 61 is about 7.4, since the pK_C for 56a is 10.42.

Anion 61 may react by three different pathways: O-protonation to the lactim 64; N-protonation to the lactam; bromine attack leading to the dibromo product. If O-protonation is faster than N-protonation (which appears reasonable since the negative charge of 61 is largely on oxygen[82,83b]) and if bromine attack is also faster than N-protonation,

then the kinetic results appear to make sense. Under the above conditions, the second equivalent of bromine may be consumed faster than expected (from the study of the bromination of 56a) and the prior attack of bromine on 2-pyridone 55a be overall rate-limiting.

The rate profile for the process (64 $\rightleftharpoons$ 61 $\xrightarrow{Br_2}$ 58a) may be simulated from the estimated pK_D 7.4 (see above) for 64 $\rightleftharpoons$ 61 and also the known bromination rate constant of 61 6.0×10^8 $M^{-1}sec^{-1}$ (Table XXI) as represented by the dashed line in Figure 22. The rate constants given by $k_8K_D/[H^+]$ are greater than k_1 2.2×10^4 $M^{-1}sec^{-1}$ for bromination of 2-pyridone, it is possible that the slow step in the dibromination is the initial attack of bromine on 2-pyridone.

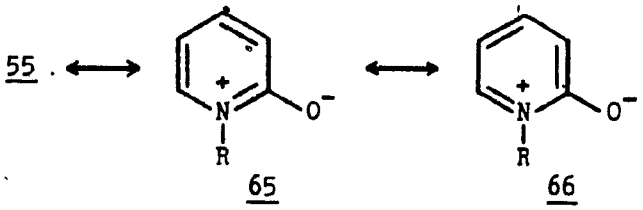
In summary, the dibromination of 2-pyridone at pH 2-6 does not appear to occur via the lactam 3-bromo-2-pyridone since this requires the observed rate constant to be $\sim 1.6 \times 10^3$ $M^{-1}sec^{-1}$. However, bromination via the lactim of 3-bromo-2-pyridone sets the observed rate of 2.2×10^4 $M^{-1}sec^{-1}$ as the slow step of the reaction and suggests that the pathway 64 $\rightleftharpoons$ 61 $\xrightarrow{Br_2}$ 58a may be occurring. This situation would have never been detected without considering consecutive second-order conditions. It may be noted that anomalous mode of dibromination appears to be involved in the case of uracil also.[49a,c]

Reactivities

In a later chapter (IV) the reactivities of various phenoxides are correlated with substituent constants. There it will be seen that the largest deviations from the correlation line are those of 2-pyridone,

its N-methyl derivative, and the N-methyl 4-pyrimidones. Apparently there is some real difference in the reactivities not simply accountable by ortho versus para product ratios. One possibility is that there is some prior complexation between the substrate and bromine. Such complexation occurs in the case of 4-methoxypyridine, as discussed below, and has also been observed in the fluorination of the trimethylsilyl ether of 2-pyridone.[92] Thus, complexation in the bromination of 2-pyridones should be considered as an explanation for the deviation.

The idea that pyridones may be considered as substituted phenoxides has been used earlier. Acheson[93] stresses the contributions to the structures of 2-pyridones from the dipolar valence-bond forms 65 and 66.

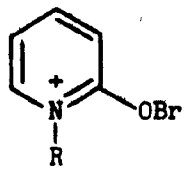


65 66

a R = H; b R = CH_3

These contributions can account for various properties of 2-pyridones, including the predominance of the tautomer 41 over 42 in aqueous solution.[68] Seen in this light 2-pyridone may be considered as a phenoxide ion bearing an ortho azonium nitrogen (=N^+—),[94] and Katritzky et al. have employed this type of approach in discussing reactivities of 2- and 4-pyridone in hydrogen-exchange reactions at elevated temperatures.[85]

These dipolar structures serve to strengthen the possible existence of the complex 66 which may account for some of the variations in the Hammett correlations (Chapter IV).



67

Moreover, a simple rearrangement of the hypobromite complex 67 may attractively explain the high ortho/para ratio in the bromination of 2-pyridones.

Mechanism

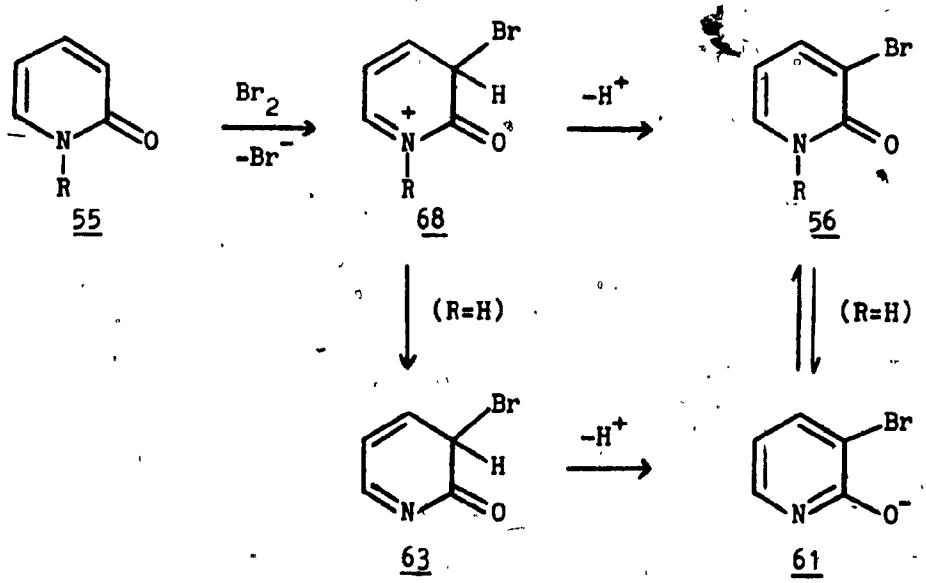
The simplest mechanism consistent with the data for 2-pyridones (55a,b) is shown in Scheme VII. It involves preferential attack of bromine at the 3 position of the pyridone 55 followed by deprotonation of the cation 68 to yield the monobromo product 56. The azacyclohexadienone 63 may well be involved in the bromination of 2-pyridone (55a), even though its concentration is never high enough (for long enough) to be observed.

In this laboratory cyclohexadienones have recently been observed in the bromination of simple alkyl phenols.[95] However, intermediates containing electron-withdrawing groups are not detected, nor are dienones resulting from ortho bromine attack; apparently they tautomerize too rapidly. It is entirely reasonable that the same should be true of the azadienone 63.

Assuming, then, that Scheme VII is followed, 1-methylpyridone (55b) simply reacts via the two-step pathway: 55b ⟶ 68b ⟶ 56b. For the parent, 2-pyridone (55a), the intermediate 68a, in equilibrium with 63a,

may breakdown directly to 56a or via 63a, depending upon the pH. All things considered, the mechanism shown in Scheme VII best represents the reaction of bromine with 55a and 55b at high acidity.

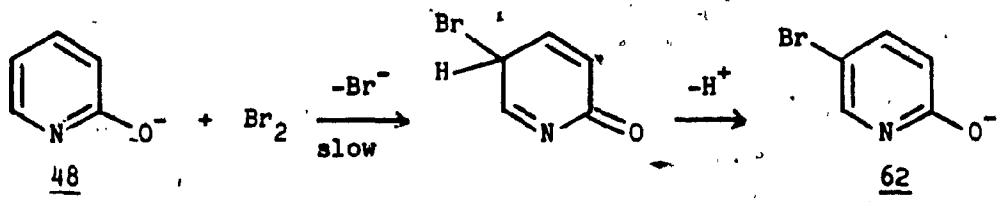
Scheme VII. Mechanism of Bromination of 2-Pyridones in Aqueous Acid.



a R = H; b R = CH_3

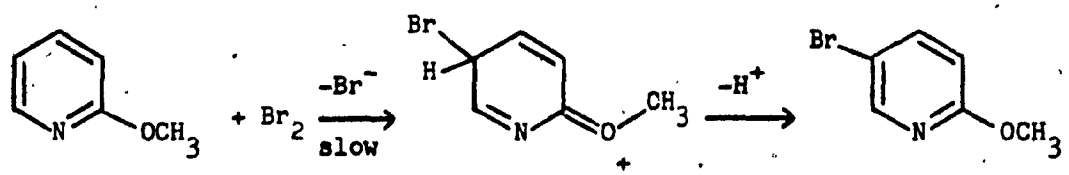
At higher pH 2-pyridone (55a) appears to react with bromine via its anion, principally at C-5 (Scheme VIII). For the simplest mechanism there is no apparent need to invoke complexation. The argument being that the pyridoxide is much more reactive than the dienone intermediates formed which in a fast step decompose to products. Also, since $-O^-$ substituent is strongly para directing (by analogy with phenoxides), it seems reasonable that 5-bromo-2-pyridone is the major product of monobromination.

Scheme VIII. Mechanism of Anionic Bromination of 2-Pyridone in Aqueous Solution.



48 62

The bromination of 2-methoxypyridine proceeds at a rate appropriate to an aza substituted anisole (see later) and leads to the formation of the 5-bromo derivative exclusively. Accordingly the reaction most likely involves bromine attack at the 5 position followed by the relatively fast deprotonation of cation 69.



59 69 60

Disubstitution

In the case of 2-pyridone and N-methyl-2-pyridone, disubstitution was a problem more evident at pH < 1. At these acidities the 3-bromo derivatives are more reactive because of lower protonation pKs and therefore more of the substrate being present in the neutral form. Factors up to 13 for 41 versus 56a are offset by K values (Table XXI)

which are different by a factor of 1000 or more. The same is true for the methyl derivative which was found to be dibrominated in 0.1 M perchloric acid.

Similarly for pH > 6.5, it can be seen, from Figure 21, that the rate constants are higher for the monobromo derivatives causing k_2^{obsd} to be greater than that of 2-pyridone at a given pH. Thus, the dibromination of 41 in basic media is understandable.

Even in the range 1 < pH < 4, the ratio of reactivities of 41 versus 56a is not large at 13:1. Thus, when 93% of the bromine has been consumed, the reaction rates for the two become comparable and the brominated derivative can compete for the remaining bromine to form the 3,5-dibromo-2-pyridone (58). For their respective N-methyl derivatives 55b and 56b, the ratio of reactivity is 17:1. Similarly, the bromination rates for the parent and monobrominated product become comparable after 94.5% reaction. Qualitatively this demonstrates the possibility of dibromination which was observed in the bromination of 55 carried out in buffer (pD 3.5) in NMR tubes.

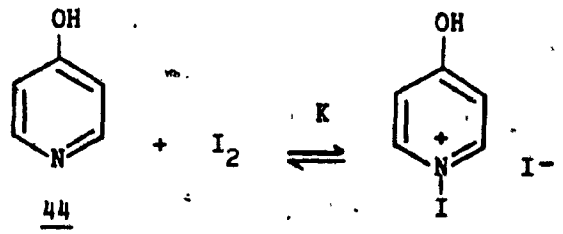
4-PYRIDONE AND DERIVATIVES

Reaction Products

Unlike 2-pyridone, the C-3 and C-5 of 4-pyridone are equivalent. Because of this symmetry, a product study was unnecessary. Dihalogenation in the 4-pyridone system appears to be more facile in all the pH regions studied. However, if special conditions are maintained, a resonable yield of 3-bromo-4-pyridone may be isolated. But, there is always > 20% yield of the dibromo compound. Thus, a competitive second-order reaction seems functional under the usual aqueous conditions. NMR spectroscopy was used in the differentiation of the product mixture.. The NMR data for 4-pyridones is reported in Table XXIII.

3-Bromo-4-pyridone reacts with bromine to form the 3,5-dibromo-4-pyridone in excellent yield. This reaction was used during the synthetic procedures to determine the presence of 3-bromo-4-pyridone among the unwanted oils and by-products from reaction of 4-substituted-3-bromopyridines. IR spectroscopy is the better technique in identifying this dihalo product.

4-Methoxypyridine reacts with bromine only to form a complex; no nuclear bromination was detected. This implies that the hydroxy tautomer 44 should only complex with bromine and otherwise be unreactive. In fact, in aprotic solvents, such as methylene chloride where 4-pyridone exists mostly in the pyridinol form, an iodine complex is formed with this substrate.[96]



44

Table XXIII. NMR Parameters for 4-Pyridone and Derivatives.[a]

Substituent on Pyridine (Medium)	Chemical Shifts δ H-2	H-3	H-5	H-6	CH_3	Coupling Constants (Hz)
4-OH [74a]	8.5	7.4	7.4	8.5	—	$J_{2,3} = J_{5,6} = 7.6$
1-Me [74a]	8.4	7.4	7.4	8.4	4.2	$J_{2,3} = J_{5,6} = 7.6$
3-Br (D_2O/DSS)	8.82	—	7.33	8.46	—	$J_{5,6} = 7.6$ $J_{2,6} = 1.2$
1-Me-3-Br Hydrobromide (D_2O/DSS)	8.64	—	7.13	8.23	4.11	$J_{5,6} = 7.0$ $J_{2,6} = 2.4$
4-OMe (D_2O/DSS)	8.67	7.22	7.22	8.67	4.07	$J_{2,3} = J_{5,6} = 5.0$ $J_{3,6} = J_{2,5} = 1.5$
4-OMe-N-oxide (D_2O/DSS)	8.62	7.49	7.49	8.62	4.15	$J_{2,3} = J_{5,6} = 5.0$ $J_{2,5} = J_{3,6} = 2.5$
4-OMe Bromine Complex ($CDCl_3$/TMS)	8.68	7.19	7.19	8.68	4.07	$J_{2,3} = J_{5,6} = 5.0$ $J_{2,5} = J_{3,6} = 2.0$

[a] This work unless otherwise referred. The standard reference in deuterium oxide was sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS), that in deuteriochloroform was tetramethylsilane (TMS).

Kinetic Studies

Bromination of 4-pyridone and its derivatives in 1.00 M aqueous KBr at 25°C, followed second-order kinetics. The data reported in Table XXIV, spanning the region 0 < pH < 8.8, clearly show that the pseudo-first-order rate constants are linearly dependent on the substrate concentration and thus give the same value for the observed second-order rate constant. The data are pictorially represented in Figure 23.

The second-order rate constants (k_2^{obsd}) were obtained as outlined earlier (page 103). For the sodium salt of 4-pyridone, the data were analyzed directly for second-order behaviour with no corresponding k_1^{obsd}. Following this direct second-order analysis and correcting for the available bromine, the k_2^{obsd} show identical pattern in the overall rate profile. This is further evidence that the reaction is second-order.

At high acidity (pH < 3 < pK_A) 4-pyridone showed a decrease in rate with increasing acidity (Figure 23). The term $K_C/[H^+]$ in equation II.8 is very small in this region and so equation II.9 applies. Since there is a decreasing trend in the second-order rate constants, it can be deduced that no bromination is occurring on the protonated form of the substrate, therefore the term $k_3[H^+]/K_A$ disappears from expression II.10. Thus, equation II.11 is applied for pH < 3. The fit of this equation to the data is compelling evidence that 4-pyridone reacts as its free base in the pH region (0-4.5).

For pH > 5, the term k_1 in equation II.5 is very small and equation II.12 is applied for 4-pyridone: suggesting reaction upon its anion 49.

Table XXIV. First- and Second-Order Rate Constants for the Bromination of 4-Pyridone and Derivatives in Aqueous Solution.[a]

pH	$[PHO]_o \times 10^5$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	k_2^{obsd} $M^{-1}\ sec^{-1}$
4-Pyridone[b]				
1.12[c]	153[d]	500		44.8
1.45[e]	200	500	0.0102	88.5
2.08	38.2[d]	500		426
	76.5[d]	500		400
	153[d]	500		397
2.35	76.5[d]	500		844
3.17	76.5[d]	500		3720
3.30	200	500	0.410	3580
3.80	100	500	0.371	6630
4.90	100	500	0.614	11000
5.52	100	500	0.683	12200
5.56	100	500	0.852	15200
6.24	100	500	2.06	36800
6.50	100	500	2.14	38300
6.93	100	500	6.27	113000
7.40	200	500	33.1	293000
7.92	100	500	39.1	738000
8.74	50.0	250	113	6710000
1-Methyl-4-pyridone[f]				
1.10[g]	250	500	0.598	41.5
2.25	125	500		597
	500	500		598
3.12	50.0	500	0.0888	3360
3.31	50.0	500	0.113	4280
3.96	50.0	500	0.253	9560
4.96	50.0	500	0.308	11600

Table XXIV. Continued.

pH	$[PHO]_o \times 10^5$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	k_2^{obsd} $M^{-1}\ sec^{-1}$
1-Methyl-4-pyridone[f]				
5.97	50.0	500		13300
	75.0	500		13200
6.92	50.0	500		12800
3-Bromo-4-pyridone[h]				
0.08[i]	100	250	0.00171	29.9
0.66[j]	50.0	250	0.00260	92.9
1.90	50.0	250	0.0130	465
2.37	25.0	250	0.00784	592
3.00	50.0	250	0.0224	800
3.41	25.0	250	0.0121	917
4.03	25.0	250	0.0184	1390
4.75	12.5	250	0.0145	2465
5.26	25.0	250	0.100	7600
	50.0	250	0.220	7870
5.95	25.0	250	0.295	22300
6.25	25.0	250	0.508	38300
7.18	12.5	250	3.04	521000
	25.0	250	6.60	502000
7.61	25.0	250	15.2	1180000
8.00	25.0	250	35.4	2850000
3-Bromo-1-methyl-4-pyridone[f]				
0.50[k]	200	500	0.00389	43.9
1.00[l]	200	500	0.0119	114
1.50	80.0	500	0.0106	241
2.00	120	500	0.0250	369
	200	500	0.0449	391
	280	500	0.0618	382

Table XXIV. Continued.

pH	$[PHO]_o \times 10^5$ M	$[Br_2]_o \times 10^7$ M	k_1^{obsd} sec^{-1}	k_2^{obsd} $M^{-1}\ sec^{-1}$
3-Bromo-1-methyl-4-pyridone[f]				
3.34	200	500	0.0567	494
4.91	200	500	0.0658	573
6.28	200	500	0.0644	562
7.32	80.0	500	0.0263	602
8.50	200	500	0.0476	537

[a] Solutions were 1.00 M in KBr and total ionic strength of 1.01 M (0.01 M for the buffer) unless otherwise specified. Temperature was 25°C. All rates are the average of three or more runs each of which has a correlation coefficient better than 0.9995.

[b] The substrate was introduced as the nitrate salt unless otherwise specified.

[c] [HBr] + [KBr] = 0.9758 M.

[d] The substrate was introduced as the sodium salt taken to be the dihydrate.

[e] $[Br^-]$ = 1.035 M.

[f] Substrate introduced as its hydrobromide.

[g] [HBr] + [KBr] = 1.000 M.

[h] Free-base form of the substrate was used.

[i] [KBr] = 1.000 M, $[H_2SO_4]$ = 1.0545 N.

[j] [KBr] = 1.000 M, $[H_2SO_4]$ = 0.3118 N.

[k] [HBr] + [KBr] = 1.3150 M, p[HBr] = 0.50.

[l] [HBr] + [KBr] = 1.1012 M, p[HBr] = 1.00.

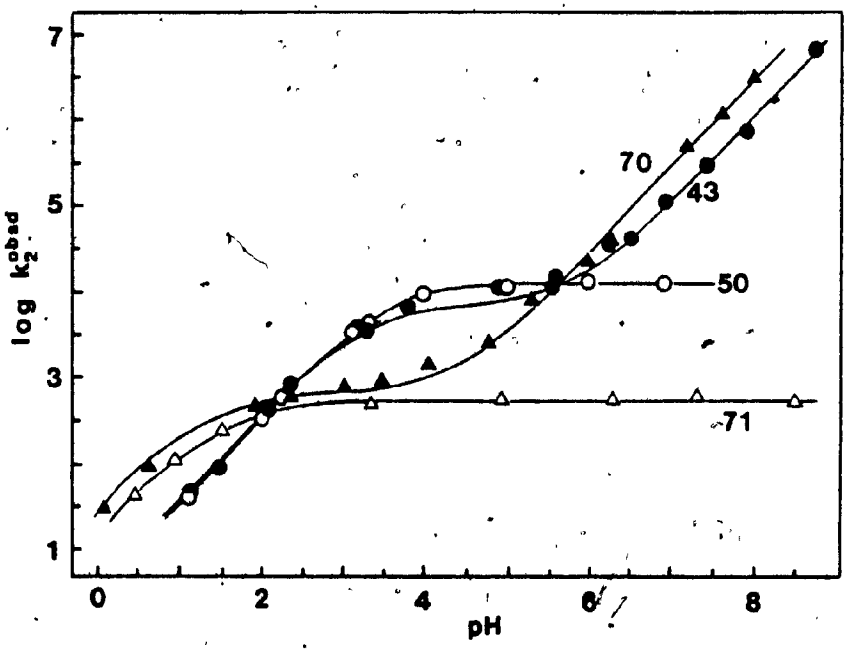


Figure 23. Rate profiles for the bromination of 4-pyridone (43, ●), 1-methyl-4-pyridone (50, O), 3-bromo-4-pyridone (70, ▲), and 1-methyl-3-bromo-4-pyridone (71, Δ). The curves were drawn using the parameters in Table XXV (see text).

Table XXV. Summary of Constants for the Reaction of Bromine with 4-Pyridones in Aqueous Solution.[a]

4-Pyridone Derivative	pK_A	pK_C	k_1 M^{-1} sec^{-1}	k_2K_C sec^{-1}	k_2 M^{-1} sec^{-1}
___	3.27	11.09	7000	0.0110	1.35×10^9
1-Methyl-___	3.58[b]		12800		
3-Bromo-___	1.37	9.46	650	0.0287	8.28×10^7
1-Methyl-3-bromo-___	1.58[b]		549		

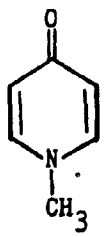
[a] Parameters used to draw profiles in Figure 23. pK_A from Table XVII.
[b] Fitted.

The curves for 4-pyridone and 3-bromo-4-pyridone in Figure 23, were plotted using equation II.14 derived from equation II.8 assuming no bromination on the protonated form of the substrate.

$$k_2^{obsd} = \frac{(k_1 + k_2K_C/[H^+])}{(1 + K_C/[H^+] + [H^+]/K_A)} \qquad \text{II.14}$$

In the range $3.5 < pH < 5.5$ the full form of the expression is necessary because of the small distinction between the values of the terms k_1 and $k_2K_C/[H^+]$ for 4-pyridone. The situation is similar for the 3-bromo derivative in the interval $2 < pH < 4$. The plots for the N-methyl derivatives follow equation II.11 given earlier. For the substrates containing an ionizeable hydrogen, both K_A and K_C were assumed to be invariant from their literature value. The fitted parameters derived by employing equations II.11 and II.14 are listed in Table XXV.

The N-methyl derivative 50 reacts via its free base with a decrease in rate below pH 2.5 due to increasing concentration of its protonated form (see Figure 23). N-methyl-3-bromo-4-pyridone 71 likewise reacts via its free base as inferred from the similarity in the rate profiles of 50.



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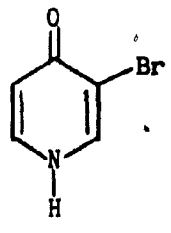

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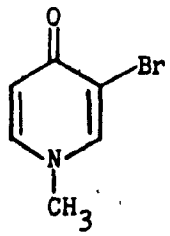

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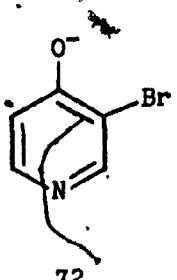


72

The plot of 3-bromo-4-pyridone 70 is similar to that of the parent

substrate 43. Employing the same arguments as above, it seems that 70 reacts via its free-base form at pH < 3, while anionic reaction is dominant for pH > 3.

Reactivities and Mechanism

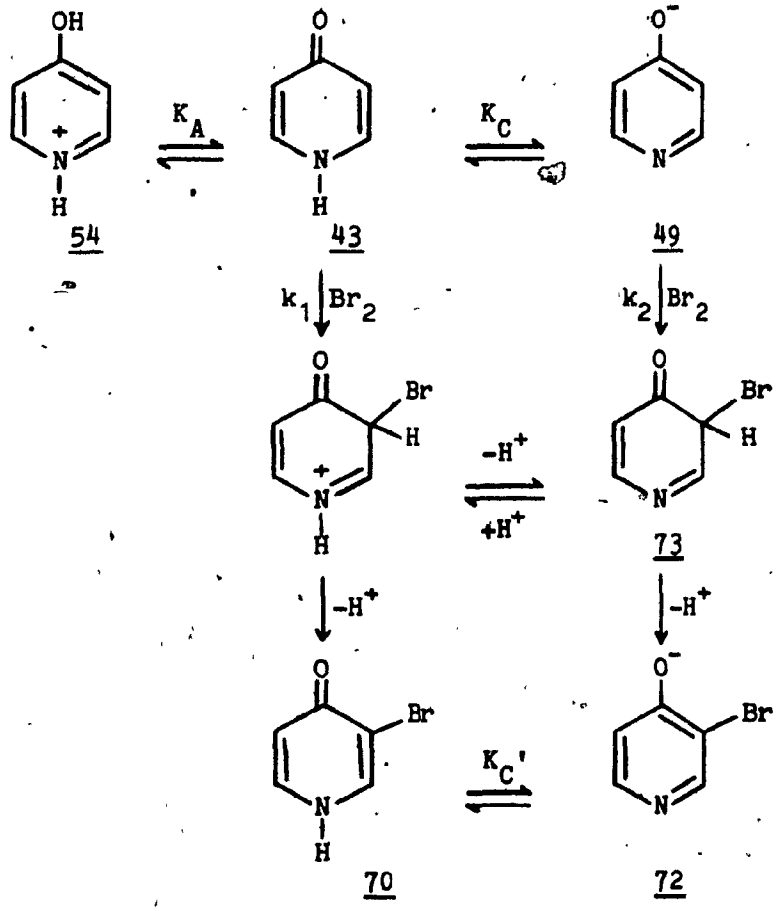
From Table XXV, the similarity in k_1 for 4-pyridone (43), 7.00 X 10^3 M^{-1} sec^{-1} as compared to 1.28 X 10^4 M^{-1} sec^{-1} for the 1-methyl derivative (50) is evidence that 4-pyridone is reacting via its lactam form (structure 43) for pH < 4.5. If it were to react as 4-pyridinol (44) one would expect it to form a complex with bromine, by analogy with its behaviour towards iodine[96] and the formation of the 4-methoxypyridine:bromine complex. Such complexes suppress nuclear bromination.

At the highest pH values, the kinetics for 4-pyridone (43) demonstrate the reactivity of bromine and perhaps tribromide, but not hypobromous acid or its anion. The reactivities of these last two forms of bromine, if significant, would have altered the observed rate constants from the rate profile. Hypobromous acid would show a decreasing rate for increasing pH because of its H^+ ion dependence (equation I.18). For pH 8.75, bromine, tribromide, hypobromous acid, and hypobromite ion are in sufficient amounts: 3.5%, 55.9%, 18.8%, and 21.8% respectively, to be able to react with the substrate, but no deviations were observed in the rate profile. This lack of deviations (noted in other work also) supports our method of correcting for these species (equation I.21).

Of all the pyridones reported in this thesis, only the 3-bromo-4-pyridones (70 and 71) show anomalous behaviour: the parent 3-bromo-4-pyridone being slightly more reactive than its N-methyl derivative. This is presently unexplainable. Furthermore, the anion 72 reacts at a rate five times less than the anion of 5-bromo-2-pyridone for bromination alpha to the carbonyl. This rate, considering no other interaction, should have been comparable for both substrates.

The simplest mechanism consistent with the data is shown in Scheme IX. This is very similar to the one proposed earlier for 2-pyridone (page 121).

Scheme IX. Mechanism of Monobromination of 4-Pyridone and its Anion.



There is no evidence in the kinetic study to suggest that intermediate 73 loses a proton to go directly to the anion 72. This process is included for completeness since in the dibromination of 4-pyridone (see below) the second bromination step occurs upon the anion of 3-bromo-4-pyridone at pH > 6. Logically it appears more expedient for 73 to go directly to 72 rather than, for instance, isomerize to 70 and then equilibrate to give 72.

Dibromination

From the plots in Figure 23 it becomes understandable why monobromination of 4-pyridone (to 70) is so difficult. 3-Bromo-4-pyridone is more reactive than 4-pyridone itself for pH < 2.3 and pH > 5.5. Frustrating as it was, there would have been no planned synthesis of 70 without knowledge of the reactivity profiles for both substrates. The aqueous region where bromination was expected to lead mainly to 70 was 2.3 < pH < 5.5. Only at these pHs is 4-pyridone actually more reactive towards bromine than 70 (Figure 23). In order to achieve a larger difference in rates, the temperature for monobromination was scaled down to zero Celsius with satisfactory results (see Experimental).

The sodium salt of 4-pyridone was also brominated at pH > 5. Kinetic data obtained under second-order conditions (2:1 of bromine:substrate) gave the values of k_2^{obsd} shown in Table XXVI and plotted in Figure 24. Attempts to obtain rate constants under pseudo-first order conditions gave anomalous traces: the first 10% of

the bromine disappearing about ten times faster than the remaining 90%. This is probably due to an impurity (~1%) in the sodium salt (since the substrate excess is ten-fold).

The rate constants in Table XXVI are about half those for the same region obtained under pseudo-first order conditions (Table XXIV and Figure 23). This again indicates successive brominations are occurring. The data in Table XXVI was obtained by analysis assuming one mole of substrate consumes one mole of bromine. However, because of successive bromination two moles of bromine are consumed per mole of substrate:

$$S + Br_2 \xrightarrow{k_2} I \xrightarrow{Br_2} \text{products}$$

Therefore, the observed rate constants are 2 X k_2. However, the analysis of the data obtained under second-order conditions take this into account and so gives a lower value.

Table XXVI. Second-order Rate Constants for the Dibromination of Sodium 4-Pyridoxide Dihydrate.[a]

pH	$[PHO^-]_o$ X 10^7 M	$[Br_2]_o$ X 10^7 M	k_2^{obsd} X 10^{-4} M^{-1} sec^{-1}
6.52	250	500	1.96
7.37	250	500	10.1
7.61	250	500	15.9
8.30	250	500	81.9

[a] [KBr] = 1.000 M at 25°C. Data was analyzed as second-order of the type A = B = $[Br_2]_o$. Correlation coefficients are all > 0.9995. Each value is the average of at least three runs and corrected for the amount of free bromine (equation I.21).

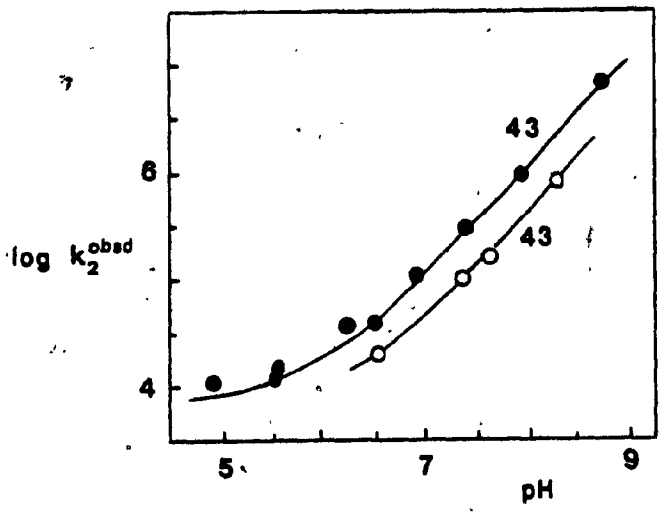


Figure 24. Plots of second-order rate constants (log k_2^{obsd}) versus pH for the bromination under pseudo-first-order conditions of 4-hydroxypyridinium nitrate (●) and under conditions of dibromination for sodium 4-pyridoxide dihydrate (O). Data was taken from Tables XXIV and XXVI.

Summary

The kinetics of bromination of 2- and 4-pyridones point to the reactivity of the lactam form at pH < 5. This is corroborated by similar reaction rates and rate profiles of the respective N-methyl derivatives. The ortho preference for bromination of the N-methyl and 2-pyridone may be explained by formation of a hypobromite and rearrangement.

The rate constants of 2-methoxypyridine, which simulates the reactivity of the lactim form of 2-pyridone, is 10^3 times less reactive

towards bromine and gives mainly the C-5 product. In contrast, the bromination of 2-pyridone yields 78% 3-bromo-2-pyridone. Moreover, ethers of 2- and 4-pyridones form much less reactive isolable complexes,[17d,92] (which may be useful halogenating agents), and equilibrium complexes in non-aqueous media.[96] Overall, the completely different behaviour of the alkoxy pyridines provide further evidence that 2- and 4-pyridone react as the lactam tautomer and not as the lactim form.

At high pH bromination appears to occur via the anions of the pyridones, as inferred from the linear dependence of rate with $[H^+]$. Furthermore, the reactivity of these anions towards bromine appears reasonable for aza-substituted phenoxide ions.

The rate profiles of the bromo derivatives of 2- and 4-pyridones helps to clarify the facile dibromination. At high pH, since the reactivity of the bromo isomers is greater than the parent, dibromination results even under pseudo-first-orderconditions. As shown in the Appendix, dibromination elevates the rate constant by a factor of two (see Figures 22 and 24). At lower pHs, dibromination of 2-pyridone proceeds at a rate comparable to its monobromination which is, of course, greater than either bromination of 3-bromo or 5-bromo-2-pyridone. This unexpected result is explained by assuming that the second bromination of 2-pyridone proceeds via the 3-bromo-2-pyridoxide, in equilibrium with the lactim tautomer, which reacts faster than 2-pyridone in this region.

III. THE PHENOLS

The main issue behind writing this chapter was to examine the diffusion-controlled reaction. The anionic bromination of phenols approaches the diffusion-controlled limit.[53,97] For phenol itself the rate constant for this reaction was hitherto unknown.

One of the criteria, for a diffusion-controlled process is that the reactivity of a substrate is so great that different electrophiles will react with it at virtually the same rate. The iodination of phenoxide[98] is 6.0 X 10^8 M^{-1} sec^{-1}: a value close to its bromination (see later). Encounter-controlled rates are important in elucidating geometry of transition states.[99] Equations determining this rate relative to the apparent rate have been developed[103] and Schurr[104] has gone as far as calculating the amount of reactive surface for two spherical reactants from the apparent rate constants. Other diffusion-rate constants have been employed in the calculation of bond distances in the activated states.[105] Although it may appear unprofitable to calculate such fast reaction constants, which are very similar in magnitude, it is of importance to calculate a series of these at different viscosities to obtain angular constraints:[104] to probe the transition state further.

Direct determination of diffusion-controlled rate constants is

generally not possible due to the speed of the reaction. However, using competitive-second-order conditions, the apparent rate may be reduced by factors of 100 or more. Therefore, the rate constants may be determined by the stopped-flow method. Additionally a pH-rate profile of the apparent second-order rate constants, obtained from competitive-consecutive second-order rates, may give information about processes which are out of reach of pseudo-first-order kinetics. A glimpse of this phenomenon was seen earlier in the dibromination of 2- and 4-pyridones. With these ideas in mind, tribromination of phenol was also carried out with interesting results!

To understand the total process of bromination of phenol, the bromination of various bromo isomers were also studied in aqueous solution. Furthermore, the rate constants for some of the bromophenols that were studied previously under different conditions were obtained under standard conditions. Thus, regardless of whether the isomer had been previously brominated or not, its bromination in aqueous molar KBr was conducted. The reported kinetic results, for a specific isomer, serve as a comparison. A high concentration of KBr was used, as for the case of the pyridones, in the expectation that very fast processes would be incurred by the anions. Under these conditions most of the bromine is in the form of Br_3^- and so the apparent rate is generally reduced.

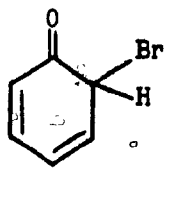
The emphasis is on the anionic bromination because these aromatic substrates are the pivot point in the correlation of the reactivity in the bromination of the pyridones and pyrimidones.

HALOGENATION

Halogenation studies, in general, are particularly important for the biochemical approach to develop radiopharmaceuticals.[106,107] The neutron deficient isotopes iodine-123 ($t_{1/2}$ = 13.3 hr) and bromine-77 ($t_{1/2}$ = 56 hr) find increasing interest for in-vivo applications in nuclear medicine. It has often been pointed out that bromine isotopes have some advantages over iodine isotopes.[106] Phenol, serving as a model substrate in this field, has been radiobrominated with bromine-77[106] or iodinated with iodine-123[107] in aqueous solutions.

Halocyclohexadienones are formed in the halogenation of phenols.[95,98,108-110] Their ketonic structures have been established conclusively by modern spectroscopic methods.[109,111,112] However, there is a paucity of information on such intermediates which are derived from unsubstituted or monosubstituted phenols.[95,110] Only the 2,5-cyclohexadienones of type 74 and 77 have recently been detected in this laboratory.[95] For instance 74 has a half-life of 46 msec at pH 2-5,[95] while the shorter-lived 2,4-cyclohexadienones such as 75 and 76 can only be postulated as intermediates.

74



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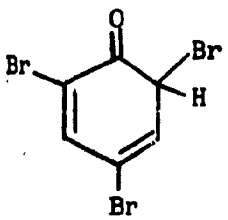

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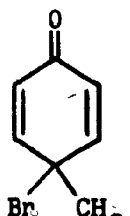

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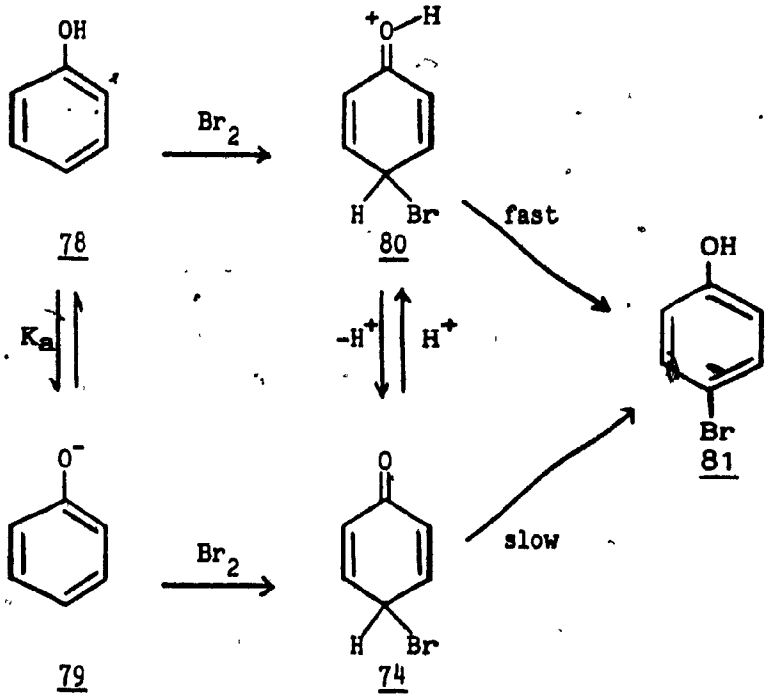
From the kinetic rate profiles for the decomposition of 74 at high acidity, it may be inferred that protonation on oxygen, on these

intermediates, increases the rate of decomposition to products.[95] This decomposition of 74 exhibits general acid and base catalysis.



In acetic acid phenol (78) undergoes monobromination mainly at C-4 (95%) with a small percentage of C-2 bromination.[113,114] A similar result was found in the present work for reaction in aqueous acid. Dibromination and even tribromination, depending on the amount of added bromine, can also be achieved. For less than equimolar ratios of reactants, as the pH is increased to neutrality and beyond, polybromination occurs[115] and can be quantitated (see Table XXVII).

Postulated mechanisms for the halogenation of phenols are generally similar,[98,116] in that they are all believed to involve halocyclohexadienones. There is at present no reason to challenge these mechanistic pathways. Dubois et al.[116] have demonstrated three

variants of a general mechanism for the study of the role of bromine and tribromide ions. The proposed pathway is outlined below:

$$Br_2 + Br^- \underset{}{\overset{K'}{\rightleftharpoons}} Br_3^- \qquad \text{I.16}$$

$$ArH + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHBr^+ + Br^- \qquad \text{III.1}$$

$$ArH + Br_3^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ArHBr^+ + 2\,Br^- \qquad \text{III.2}$$

$$ArHBr^+ \xrightarrow{k_3} ArBr + H^+ \qquad \text{III.3}$$

In the present case the last (irreversible) step is the decomposition of the protonated dienone, $ArHBr^+$ (cf. 80). Assuming a steady state on this intermediate, Dubois[116a] derived the general form for the apparent rate constant:

$$k_2^{app}(1 + K'[Br^-]) = \frac{k_1k_3 + k_2k_3K'[Br^-]}{k_{-1}[Br^-] + k_{-2}[Br^-]^2 + k_3} \qquad \text{III.4}$$

The first variant comes from the assumption that $k_3 >> k_{-1}[Br^-] + k_{-2}[Br^-]^2$, that is, the formation of $ArHBr^+$ is rate determining. Then

$$k_2^{app}(1 + K'[Br^-]) = k_1 + k_2K'[Br^-] \qquad \text{III.5}$$

and there should be a linear dependence on bromide ion. This is precisely the situation encountered with some substituted anisoles.[116a]

The second case is that where there is no reaction via tribromide ion. Equation III.2 is nonexistent and

$$k_2^{app}(1 + K'[Br^-]) = k_1 \qquad \text{III.6}$$

Bell[53] has found no tribromide ion dependence in bromination of phenol in accordance with equation III.6.

The case where there may be an inverse bromide ion dependence is if the breakdown of $ArHBr^+$ were rate-determining (i.e. $k_3 \ll k_{-1}[Br^-] + k_{-2}[Br^-]^2$). In this case

$$k_2^{app}(1 + K'[Br^-] = (k_3k_1)/(k_{-1}[Br^-]) \qquad \text{III.7}$$

This situation is found in the bromination of 4-bromo-N,N-dimethylaniline.[117]

The last case considered corresponds to the situation where the breakdown of the intermediate to products and to reactants are competitive ($k_3 \simeq k_{-1}[Br^-]$) and Br_3^- is not involved. Such behaviour was found earlier for the iodination of 4-nitrophenol.[118] The appropriate equation is

$$k_2^{app}(1 + K'[Br^-]) = k_1k_3/(k_{-1}[Br^-] + k_3) \qquad \text{III.8}$$

Thus, for the case of positive or zero bromide ion dependence, formation of the complex is the rate-determining step, whereas the inverse effect of bromide ions strongly indicates that the rupture of the C-H bond, from the intermediate complex, is wholly (equation III.7) or partly (equation III.8) rate-determining. The presence or absence of primary isotope effects may also be successfully explained using this mechanism.[98,116,118]

RESULTS

Product Studies

The ortho-para isomer ratios of the monobromophenols in bromination of phenol was obtained by a gas-chromatographic technique (see Experimental). For quantitative results a calibration graph was constructed using accurately weighed mixtures of 2- and 4-bromophenol and peak-height ratios. The results are plotted in Figure 25. Bromination of phenol at different pHs and analysis of the reaction mixtures led to the results reported in Table XXVII. This table contains the results for 2-/4-bromophenol ratios in terms of ratios in peak height, which were superimposed on the calibration graph, Figure 25.

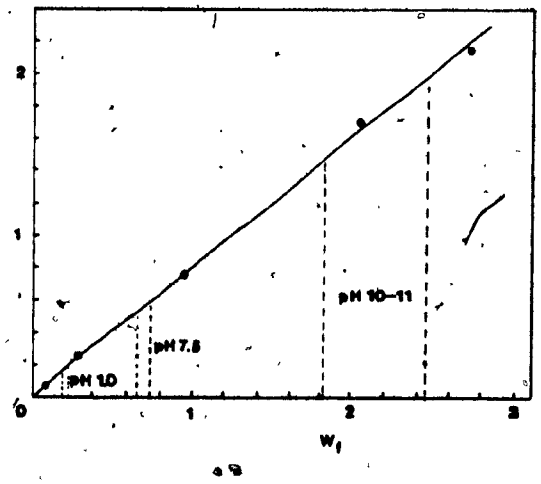


Figure 25. Calibration graph of GC results displaying the average peak-height ratios for ortho/para bromophenols (R_L) versus the average weight ratios for ortho/para bromophenols (W_f). Superimposed are the extrema of the peak-height ratios obtained after injection of the product mixtures.

Table XXVII. Results of Product Study for Phenol by Gas Chromatography.

pH	Average[a] Peak-Heights for Bromine/Phenol Ratios		Average Ortho/Para Ratios of Bromophenols[b]	Average Tribromophenol
	1:1	1:10		
1.00	0.165	0.202	0.23 ± 0.02	some[c]
7.5	0.591	0.534	0.70 ± 0.04	82%[d]
10-11[e]	1.47	1.98	2.1 ± 0.3	16%[d]

[a] Of at least three injections.

[b] Obtained from calibration graph Figure 25 (above).

[c] Refers to polybrominated phenols as visible precipitate and not necessarily tribromophenol.

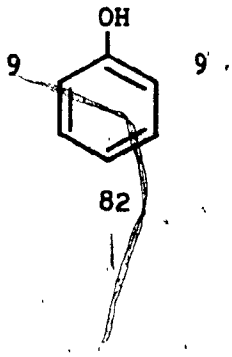
[d] Determined by dry-weight of precipitate. Yield based on $[Br_2]_o$.

[e] For 1:1 and 1:10 ratios $[Br_2]_o$ = 0.0125 M and [NaOH] = 0.02 M.

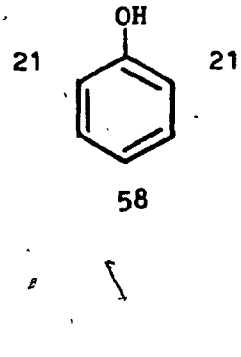
The o/p ratio at pH 1.00 is similar to that obtained earlier for reaction in acetic acid.[114] No meta bromination was detected. Meta bromination does arise in some cases but following rearrangement of the dienone in strong acid.[108b,110,113,119] Bromination of phenol in aqueous solution undergoes polybromination as can be seen from the appearance of 2,4,6-tribromophenol in Table XXVII.

The results from GC study led to the isomer distributions below which are similar to those for the radiobromination of phenol.[106]

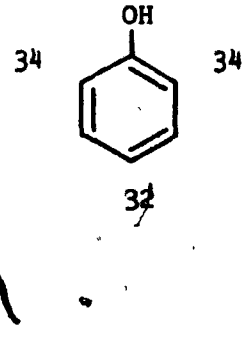
pH 1.0



pH 7.5



pH 10



The above method for determining isomer distribution of bromophenols had some disadvantages. No dibrominated phenols were detected. Secondly the experimental conditions deviated from the UV kinetic studies both in terms of quantities of reactants and in sample manipulations. Thus, a different UV experiment was devised in order to determine all the species in the mixture following the bromination reaction. This required individual wavelength and extinction coefficients of all the possible products at a specific pH and temperature of reaction. The analysis required the solution of "n" simultaneous equations ("n" is six for phenol). Clearly the use of a computer was required. Some of the UV data, for maximun wavelength absorption, for each species are reported in Table XXVIII.

UVPROS, the program written by the author to handle such a problem (see Experimental), gave results tabulated in Table XXIX. It was disappointing to see that the values differed from the GC results. These data are suggestive that there is more equality in the ortho/para ratio in bromination of phenol. However, it seems to point out that some tribromination does occur even in very acidic conditions in agreement with observed synthetic bromination. To make the data more realistic, calibration graphs much like the one portrayed in Figure 25 are required. Thus, weighed mixtures of the different isomers should be made and the UV data subjected to this computer analysis. The results for an individual or combined isomeric ratio can be plotted versus the actual amounts employed.

Table XXVIII. UV Parameters and Dissociation Constants for Phenols.

Compound	$(pK_a)^{120}$	pH	λ_{max} in nm (log ϵ)[a]
Phenol	10.00	0.77[b]	269(3.11)
		4.00	269(3.11)
		7.00	269(3.11)
2-Bromophenol	8.44	0.77[b]	275(3.30)
		4.00	274(3.30), <240(>2.51)
		7.00	274(3.30), <230(>3.00)
4-Bromophenol	9.36	0.77[b]	279(3.10)
		4.00	279(3.12), <240(>3.19)
		7.00	279(3.09), <230(>3.56)
2,4-diBromophenol	7.79	0.77[b]	286(3.23)
		4.00	286(3.31), <240(>3.18)
		7.00	287(3.27), <u>311(2.75)</u>, <u>246(3.37)</u>, <230(>3.61)
2,6-diBromophenol	6.67	0.77[b]	279(3.29)
		4.00	279(3.30), <240(>3.05)
		7.00	230(3.75), 301(3.58)
2,4,6-triBromophenol	5.93[c]	0.77[b]	<250(>2.92), 291(3.27)
		4.00	<240(>3.26), 292(3.25)
		7.00	247(3.90), 315(3.57)

[a] Underlined values refer to shoulder or inflection.

[b] [HBr] = 0.1675 M at 25°C.

[c] From this work at 25°C. Total ionic strength was 0.11 M.

Table XXIX. Concentration of Bromophenols in Bromination of Phenol and 2-Bromophenol from UV Study.[a]

pH	$[Br_2]_o$ X 10^6 M	Product Mixture [Phenol] X 10^6 M	[4-Br] X 10^6 M	[2-Br] X 10^6 M	[2,4-Br_2] X 10^7 M	[2,6-Br_2] X 10^7 M	[2,4,6-Br_3] X 10^7 M
Phenol[b]							
0.77[c]	200	19 ± 8	101 ± 9	61 ± 8	85 ± 18	110 ± 80	~0
	300	16 ± 1	35 ± 3	43 ± 1	690 ± 70	260 ± 20	10
3.98	100	121 ± 1	47 ± 2	13 ± 1	71 ± 8	110 ± 2	15 ± 5
	200	51 ± 1	101 ± 1	17 ± 1	60 ± 9	20 ± 10	210 ± 10
7.08	100	151 ± 2	10 ± 3	13 ± 4	15 ± 26	~0	249 ± 4
	200	121 ± 2	11 ± 6	5 ± 5	40 ± 30	~0	586 ± 4
	300	91 ± 1	12 ± 1	~0	36 ± 8	17 ± 3	927 ± 2
2-Bromophenol[d]							
0.08[e,f]	30			25.3 ± 0.4	124 ± 6	70 ± 10	53 ± 4
	50			6.1 ± 0.5	250 ± 10	120 ± 10	61 ± 5
0.77[c]	100			104 ± 0.1	745 ± 10	175 ± 10	40 ± 10
	200			62 ± 1	320 ± 20	400 ± 200	600 ± 100
3.98	100			131 ± 4	270 ± 40	110 ± 80	310 ± 40
	200			62 ± 0.5	490 ± 60	270 ± 70	620 ± 50
7.08	100			140 ± 1	160 ± 10	37 ± 8	4 ± 0.1
	200			89 ± 1	150 ± 20	56 ± 9	890 ± 10
	300			40 ± 1	180 ± 10	23 ± 4	1400 ± 10

[a] Medium was 1.00 M aqueous KBr unless otherwise stated. Equivalent volumes of reactants were simultaneously mixed from two syringes and allowed to react five hours. Data were obtained from the program UVPROS

[b] $[Phenol]_o = 2.00 \times 10^{-4}$ M.

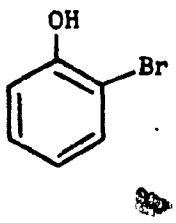
[c] [HBr] = 0.1675 M no added KBr.

[d] $[2\text{-Bromophenol}]_o = 2.00 \times 10^{-4}$ M, [e] 5.00×10^{-5} M.

[f] [HBr] = 0.8318 M no added KBr.

Kinetic Results

By using the UV stopped-flow technique it was possible to follow the bromination of phenol and its bromo derivatives (structures 78, 81-85) in aqueous solution of 1 M potassium bromide in the range $0 < pH < 7$ at 25°C.



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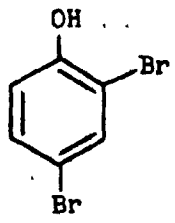

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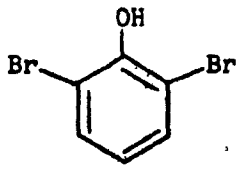

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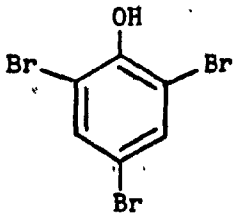

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The kinetic data, collected in Table XXX, shows that the bromination rates of these aromatic substrates is overall second order: first order with respect to substrate and first order with respect to bromine. Substrate dependence show the invariance of the second-order rate constants, which are corrected for the fraction of free bromine. Overall second-order dependence in the bromination of phenols was also observed by Bell.[53] From Table XXX the rate profiles for each phenol were drawn in Figure 26 (page 152).

Table XXX. Observed Rate Constants for the Bromination of Phenols in Aqueous Solutions.[a]

pH	$[Sub]_o$ X 10^6 M	$[Br_2]_o$ X 10^7 M	k_1^{obsd} sec^{-1}	k_2^{obsd} X 10^{-5} $M^{-1}sec^{-1}$	pH	$[Sub]_o$ X 10^6 M	$[Br_2]_o$ X 10^7 M	k_1^{obsd} sec^{-1}	k_2^{obsd} X 10^{-5} $M^{-1}sec^{-1}$
	Phenol					2-Bromophenol			
0.38[b]	500	250	13.4	4.80	0.40[b]	225	250	0.181	0.154
1.09	500	250	12.5	4.47		500	250	0.419	0.150
1.68	625	250	14.0	3.97		1000	250	0.955	0.167
2.04	1000	500	19.3	3.44	1.03	300	250	0.236	0.146
	1250	500	25.3	3.57		600	250	0.491	0.145
	1500	500	29.3	3.44	1.68	725	250	0.665	0.162
2.64	500	250	12.2	4.37	2.07	600	500	0.620	0.192
2.93	500	250	12.8	4.58	3.15	300	250	1.23	0.760
3.49	625	250	14.3	4.05	3.50	625	250	5.53	1.57
4.07	500	250	12.5	4.47	4.17	300	250	11.0	6.80
4.48	250	250	[c]	5.69	4.55	300	250	20.2	12.5
	500	250	[c]	5.63		375	250	28.0	13.6
5.01	312.5	250	[c]	7.29		500	250	38.4	13.7
	625	250	[c]	6.55	5.00	200	125	40.9	37.1
5.20	625	125	26.0	7.37	5.25	125	125	[c]	62.4
5.58	125	125	9.04	13.7	5.54	100	125	[c]	161
	250	125	17.0	12.2		125	125	104	157
5.97	125	125	18.5	28.0					
	250	125	35.5	25.4					
6.30	200	125	45.8	41.5					
6.49	125	125	47.7	72.1					
6.77	125	125	85.7	130					

Table XXX. Continued

pH	$[Sub]_o$ X 10^6 M	$[Br_2]_o$ X 10^7 M	k_1^{obsd} sec^{-1}	k_2^{obsd} X 10^{-5} $M^{-1}sec^{-1}$
		4-Bromophenol		
0.30[b]	500	250	0.121	0.0433
	750	250	0.189	0.0443
	1000	250	0.246	0.0429
1.02	1000	250	0.255	0.0445
2.40	500	250	0.182	0.0651
3.01	250	250	0.146	0.110
	500	250	0.268	0.0959
3.39	625	250	0.703	0.199
4.05	625	250	2.25	0.638
4.51	125	125	1.47	2.22
5.16	250	250	11.9	8.99
5.62	125	125	16.6	25.1
		2,4-diBromophenol		
0.15[b]	1000	500	0.0206	0.00369
1.10	1000	500	0.0540	0.00967
1.95	1630	500	[c]	0.0583
	2560	500	[c]	0.0585
	3200	500	[c]	0.0554
		2,4-diBromophenol		
2.75	1000	500	2.13	0.381
2.90	2000	500	5.45	0.471
4.00	100	250	[c]	7.24
	500	250	[c]	7.32
5.10	100	250	[c]	92.1
		2,6-diBromophenol		
0.14[b]	1000	500	0.778	0.0139
1.12	1000	500	0.373	0.0667
2.33	400	500	[c]	1.22
	500	500	[c]	1.20
	1000	500	[c]	1.18
2.85	1000	500	27.1	4.85
4.00	100	125	[c]	55.8
5.08	20	125	[c]	774
5.62	10	100	[c]	4680
		2,4,6-triBromophenol[d]		
5.62	10	400	[c]	0.567

[a] Each datum is the average of at least three runs (c-c > .9995) at 25°C and 1.00 M KBr. Ionic strength of the universal buffer was 0.01 M.

[b] Glass electrode reading. Actual $[H_2SO_4]$ = 0.500 M, H_o = 0.12.

[c] Direct second-order analysis was applied.

[d] This run is bromination of 2,6-dibromophenol 1 X 10^{-5} M with 5 X 10^{-5} M bromine where the first bromination step proceeds very much faster than the second.

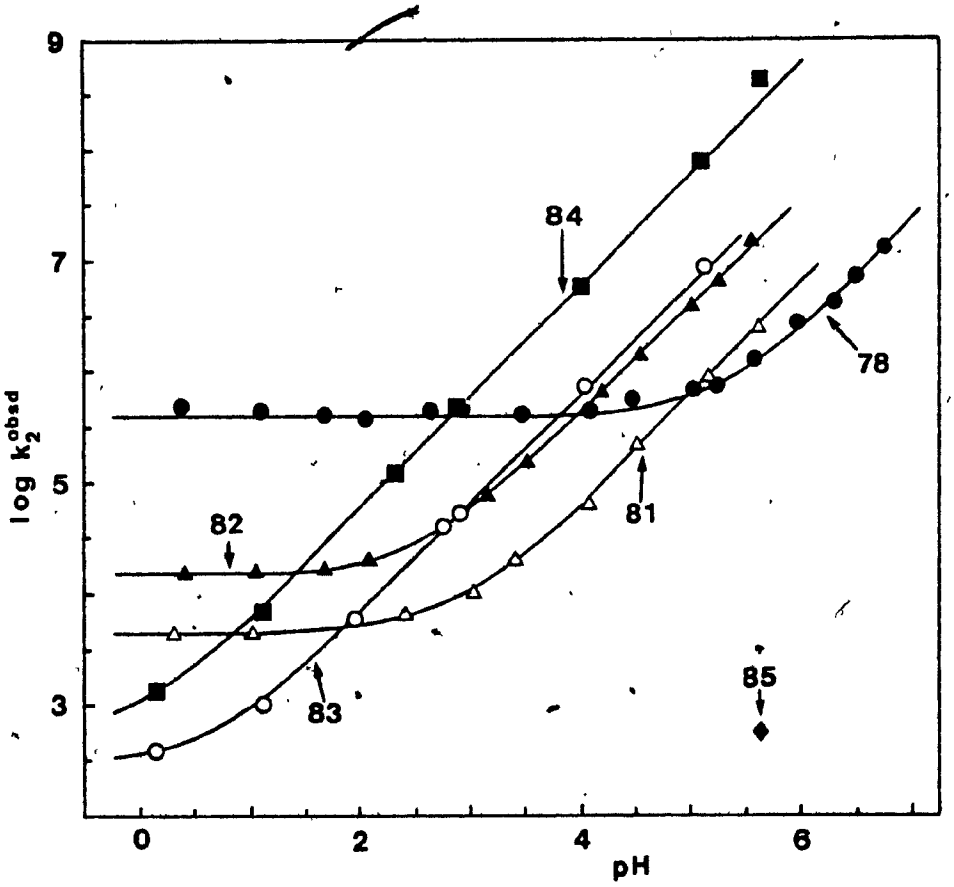


Figure 26. Rate profiles for the bromination of phenol (78, ●), 2-bromophenol (82, ▲), 4-bromophenol (81, △), 2,4-dibromophenol (83, ○), 2,6-dibromophenol (84, ■), 2,4,6-tribromophenol (85, ◆) in aqueous solution at 25°C.

The rate law assumed for the above data was:

$$-d[Br_2]/dt = k_{POH}[PHOH][Br_2] + k_{PO^-}[PHO^-][Br_2] \qquad \text{III.9}$$

where [PHOH] and [PHO^-] are the concentrations of the free-acid and anion forms of the phenolic substrate respectively, and [Br_2] the concentration of free bromine. From the rate profile (Figure 26) a protonated form of the substrate does not seem to enter into the rate law.

The constants k_{POH} and k_{PO^-} (equation III.9) may be dissected into their various components. It has been stated elsewhere[53] that the reactive forms may be phenol, phenoxide, bromine, and tribromide represented in the following paths:

$$PHOH + Br_2 \xrightarrow{k_a} C + \ldots \qquad \text{III.10}$$

$$PHOH + Br_3^- \xrightarrow{k_b} C + \ldots \qquad \text{III.11}$$

$$PHO^- + Br_2 \xrightarrow{k_c} C + \ldots \qquad \text{III.12}$$

$$PHO^- + Br_3^- \xrightarrow{k_d} C + \ldots \qquad \text{III.13}$$

Bell[53] found no reaction of tribromide ion on the neutral phenols and k_b may be assumed to be zero. For the phenoxides, however, tribromide ion reaction does occur and the highest $k_d/k_c' = 0.033$ was found for 2,4-dibromophenol.[53]

The determination of k_d is complicated and is usually ignored without affecting the overall mechanistic interpretation. Although a slope (denoted here as S_1) of k_2^{obsd} for varying $[Br^-]$ can be trivial, the analysis of it is not. In fact, Bell and Rawlinson[53] had to estimate a primary salt effect (ϕ) of 2.0 at an ionic strength of 0.20 M and an average activity coefficient ($\gamma_{\pm}$) of 0.778 at the same ionic strength. The value k_d, with these assumptions, is determined by the expression:

$$k_d = (S_1 (\gamma_{\pm})^2 [H^+]K_1)/(K_a \phi) \qquad \text{III.14}$$

where K_a and K_1 are the dissociation constants for phenol and tribromide ion respectively. In the present study this expression

should also contain a term involving the reciprocal of the viscosity (for the diffusion-controlled rate and those approaching it[97,104]) and worse estimates for $\gamma_{\pm}$ and ϕ at an ionic strength of 1.00 M.

A tribromide ion dependence study was attempted for phenoxide ion. The results are shown in Table XXXI and plotted in Figure 27. The positive slope (S_1 = 4.11 X 10^6 M^{-2} sec^{-1}) in Figure 27, demonstrates the participation of Br_3^- in the reaction with a magnitude of k_d = 8.50 X 10^8 $M^{-1}sec.^{-1}$ From the intercept the attack of phenoxide on bromine has a rate constant of k_c = 1.18 X 10^9 $M^{-1}sec^{-1}$ (calculated assuming pK_a = 10.00 for phenol). This is less than the rate of attack of 4-bromophenoxide on bromine k_c = 7.8 X 10^9 $M^{-1}sec,^{-1}$ but it must be borne in mind, that the value of Bell is extrapolated to zero ionic strength while the one in this study is at I = 1.03 M. Any direct comparison is thus of doubtful value.

Table XXXI. Bromide Ion Dependence on Bromination Rates of Phenoxide Ion at pH 6.48.[a]

[KBr] M	[KNO_3] M	$[PHOH]_o$ M	$[Br_2]_o$ M	(k_1^{obsd}) X 10^{-5} sec^{-1}	(k_2^{obsd}) X 10^{-6} [b] M^{-1} sec^{-1}
0.250	0.750	500	500	2.71	1.39
0.500	0.500	500	500	2.73	2.47
0.750	0.250	500	500	2.53	3.30
1.00	0.00	500	500	2.67	4.54

[a] At 25°C, I = 1.03 M.

[b] k_2^{obsd} was calculated from k_1^{obsd} by dividing by ([PHOH] - $[Br_2]_o$) and multiplying by the correction factor for free bromine equation I.21.

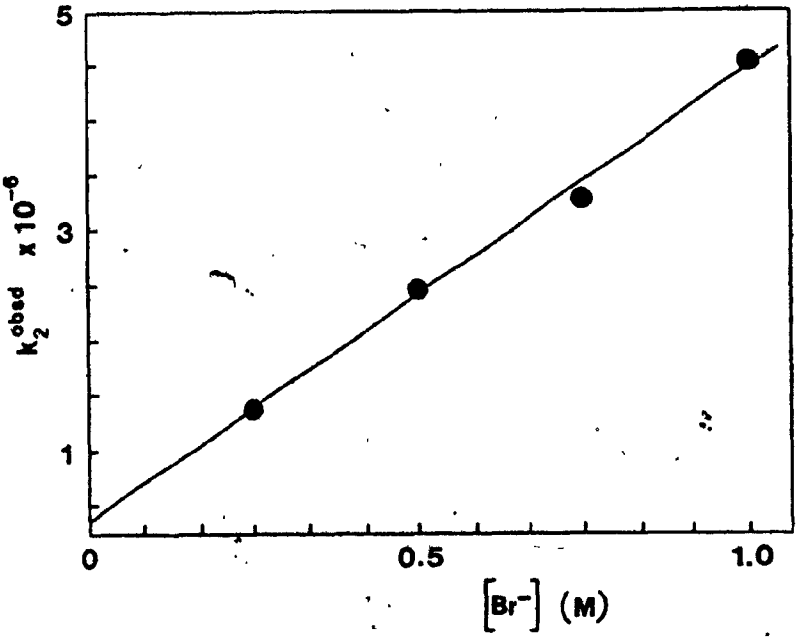


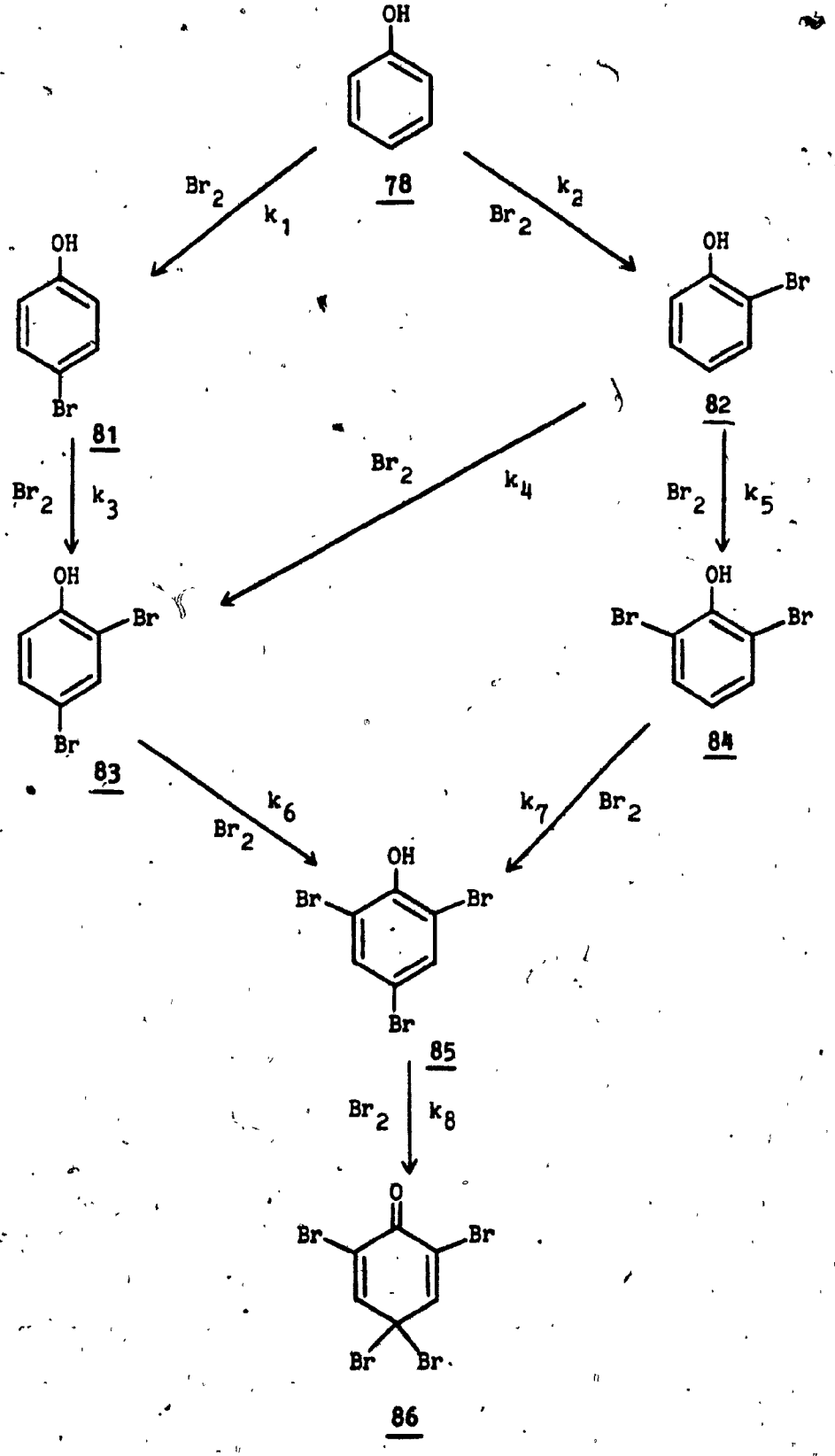
Figure 27. Rate dependence of phenoxide bromination with $[Br^-]$. The slope, intercept, and correlation coefficient are 4.11×10^6 M^{-2} sec^{-1}, 3.55×10^5 M^{-1} sec^{-1}, and 0.997 respectively.

This is the only tribromide ion study done for the phenols in this thesis. Although there is strong evidence for tribromide ion reactivity, for the more reactive substrates (phenoxides),[53] such reaction will no longer be treated apart from bromination by bromine. The weighted sum of k_c and k_d will be considered in the following discussion (equation III.15).

$$k_F = k_c + k_d\ ([Br^-]/K) \qquad \text{III.15}$$

Furthermore, so as not to confuse the reader, a unique symbolism for the rate constants will be maintained in this chapter (Scheme X below).

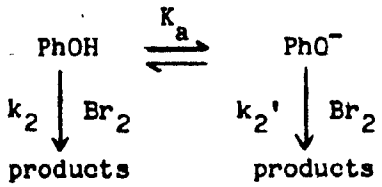
Scheme X. Pathway for Polybromination of Phenol.



We now consider the acidity dependence of the rate constants depicted in Figure 26. For each phenol, in Scheme X above, the data may be represented by:

$$k_2^{obsd} = k_2 + (k_2' K_a)/[H^+] \qquad \text{III.16}$$

where k_2, k_2', and K_a are represented by the pathway below:



The appropriate parameters for equation III.16 are listed in Table XXXII (page 158). These were employed to draw the theoretical curves in Figure 26. Analysis of equation III.16 places $k_2 = 4.1 \times 10^5\ M^{-1}\ sec^{-1}$ and $k_2' = 2.2 \times 10^{10}\ M^{-1}\ sec^{-1}$ assuming $K_a = 1.0 \times 10^{-10}$ M for phenol.

The other phenols likewise react via their undissociated form where their rate profile is horizontal. However, such rate constants for 2,4- and 2,6-dibromophenol had to be estimated for lack of data in more acidic region (pH < 0). Anionic rate constants can be easily extracted from the experimental data by analysis of equation III.16.

Table XXXII. Summary of Rate Constants for Attack of Bromine upon Phenols and Phenoxide Ions.[a]

Substrate	pK_a	Rate Constants for the Substrate		
		Total Scheme X	Neutral (k_2) M^{-1} sec^{-1}	Anionic (k_2') M^{-1} sec^{-1}
Phenol	10.00	($k_1 + k_2$)	410000	2.2×10^{10}
			(180000)[b]	
2-Bromophenol	8.44	($k_4 + k_5$)	1.5×10^{4}	1.1×10^{10}
4-Bromophenol	9.36	(k_3)	4400	1.4×10^{10}
			(3200)[b]	(7.8×10^{9})[b]
2,4-diBromophenol	7.79	(k_6)	~240	4.2×10^{9}
			(550)[b]	(1.5×10^{9})[b]
2,6-diBromophenol	6.67	(k_7)	~500	2.8×10^{9}
			(185)[c]	
2,4,6-triBromophenol	5.93	(k_8)		~2200[d]

[a] Constants used to draw rate profiles in Figure 26.

[b] Results from Bell,[53] obtained in dilute $HClO_4$ extrapolated to zero ionic strength.

[c] Result from Grovenstein et al.[98] at 2.00 M HBr and 0°C.

[d] Result estimated from one kinetic run for dibromination of 2,6-dibromophenol. Anionic bromination was assumed.

The values taken from the literature in Table XXXII are to be used and interpreted with caution. The rate constant 1.8×10^5 M^{-1} sec^{-1} for the bromination of neutral phenol has been admitted by Bell and Rawlinson[53] to be of low accuracy because it was obtained towards the limit of their technique. The value of 3200 M^{-1} sec^{-1} for 4-bromophenol has been readjusted.[49a] The value 3.2×10^9 M^{-1} sec^{-1} misprinted in the original paper[53] has often been quoted unchanged.[97] Moreover, Bell[53] and Grovenstein[98] obtained their values working over a limited range of acidity spanning one or two pH units. Worse still is their extrapolation from this small pH range to obtain their rate constants. Conditions such as ionic strength and temperature are different. Considering all these disparities, our values better represent the actual bromination rates for phenols.

Apparently the stopped-flow method is better suited for obtaining diffusion rates > 10^9 M^{-1} sec^{-1} than the bromination by electrogenerated bromine.[53] The k_2 constants for phenols in Table XXXII contain contribution from di- and even tribromination. The problem of correcting for polybromination is discussed in the next section.

In summary, tribromide ion reactivity is large for phenoxide ion. This is in part responsible for the apparently high diffusion rates shown in Table XXXII. In fact the rate constant for bromination of phenoxide 2.2×10^{10} M^{-1} sec^{-1} is a weighed sum of the reactivity of free bromine and tribromide. By substituting $k_c = 1.18 \times 10^9$ M^{-1} sec^{-1} (reactivity of bromine) and $k_d = 8.50 \times 10^8$ M^{-1} sec^{-1} (reactivity of tribromide) into equation III.15 assuming that the dissociation constant for tribromide is 0.0625 M at 1.00 M Br^-, the apparent rate constant for

this reaction (at one pH) is:

$$1.18 \times 10^{9} + (8.50 \times 10^{8}) \frac{(1.00)}{0.0625} = 1.5 \times 10^{10}\ M^{-1} sec^{-1}$$

This is in good agreement with the value of $2.0 \times 10^{10}\ M^{-1}\ sec^{-1}$ obtained from fitting the rate profile.

Polybromination: Quantitative Aspects

Having obtained all the rate profiles for phenols and its bromo derivatives facilitates consideration of the more complex reaction: one where all products and all transient intermediates must be formed in one reaction mixture. This situation obviously occurs when enough bromine is added to the substrate to produce tribromophenol quantitatively. The purpose of such a kinetic study is to uncover quantitatively the extent of polybromination and to understand how the rate of disappearance of the halogen is affected by the presence of bromocyclohexadienones.

The answer to the first part of the question is easier. Consider the tribromination of phenol with its full rate equation:

$$-(d[Br_2]/dt) = \{(k_1 + k_2)[\underline{78}] + k_3[\underline{81}] + (k_4 + k_5)[\underline{82}] + k_6[\underline{83}] + k_7[\underline{84}]\}[Br_2] \qquad \text{III.17}$$

where the rate constants and structure numbers refer to the process in Scheme X (page 156). The root of such differential equation is the function:

$$[Br_2] = 1/\{(k_2^{obsd})t + (1/[Br_2]_o\}$$

as deduced from similar processes in the Appendix for a 3:1 bromine:phenol ratio. The value of k_2^{obsd} can be either of five possible values: (1) $(k_1 + k_2)$, (2) k_3, (3) $(k_4 + k_5)$, (4) k_6, and (5) k_7. Which of these is appropriate depends on the acidity since the rate-limiting step in the polybromination is acidity dependent, as discussed below.

Under pseudo-first-order conditions, only the first term in equation III.17 is considered. The assumption being that there is no polybromination occurring. But, if the reaction is truly competitive, then even under pseudo-first-order conditions, all the terms of equation III.17 must be considered. This situation is treated under Case 1 in the Appendix with the result that $k_2^{obsd} = 3(k_1 + k_2)$. In summary, there is a potential difference of a factor of three between the pseudo-first-order rate constant and that obtained under competitive consecutive second-order conditions.

Both phenol and 4-bromophenol were polybrominated under second-order conditions to give tribromophenol. The kinetic data are listed in Table XXXIII and depicted side by side with those obtained from pseudo-first-order conditions in Figure 28. The values in Table XXXIII contain no statistical factors and, therefore, are assignable to the rate constants in equation III.17 (see Scheme X). The values of the rate constants obtained under pseudo-first-order conditions are then some factor greater than this value which can be found directly from the graph in Figure 28. As it turns out, the factor for tribromination of phenol, obtained under pseudo-first-order conditions, is not 3 as expected. This implies then that the reaction is not brominating phenol

fully to 2,4,6-tribromophenol for large excess of the aromatic substrate for pH > 5.5. This presumably results since at pH > 5.5 p-bromophenol is only slightly (ca. 2 X) more reactive than phenol. Any competition for bromine which occurs under first-order conditions (ten-fold excess phenol) is probably due to subsequent bromination of 2-bromophenol, since it is twenty-times more reactive than phenol.

Table XXXIII. Observed Rate Constants for the Polybromination of Phenols in Aqueous Solution.[a]

Tribromination of Phenol[b]		Dibromination of 4-Bromophenol		
pH	k_2^{obsd} M^{-1} sec^{-1}	pH	$[Br_2]_o$ X 10^7 M	k_2^{obsd} M^{-1} sec^{-1}
0.50[c]	2.58 X 10^3	2.87	500	7.67 X 10^3
1.00	3.91 X 10^3	3.50	250	1.60 X 10^4
1.78	5.81 X 10^3	4.05	250	3.56 X 10^4
2.73	5.98 X 10^3	4.95	125	2.92 X 10^5
3.82	3.69 X 10^4	5.08	125	3.52 X 10^5
4.08	3.23 X 10^4			
4.78	2.84 X 10^5			
5.29	5.60 X 10^5			
5.58	6.92 X 10^5			
6.10	2.35 X 10^6			
6.35	2.06 X 10^6			
7.08	1.11 X 10^7			
7.65	3.63 X 10^7			

[a] Medium was 1.00 M KBr at 25°C; $n[POH]_o = [Br_2]_o$: n = 3 for phenol, n = 2 for 4-bromophenol. Analysis was second-order of the type A = B = $[Br_2]_o$. All correlation coefficients are > 0.9995.

[b] $[Br_2]_o$ = 5.00 X 10^{-5} M for all runs.

[c] Glass electrode reading of 0.500 M H_2SO_4.

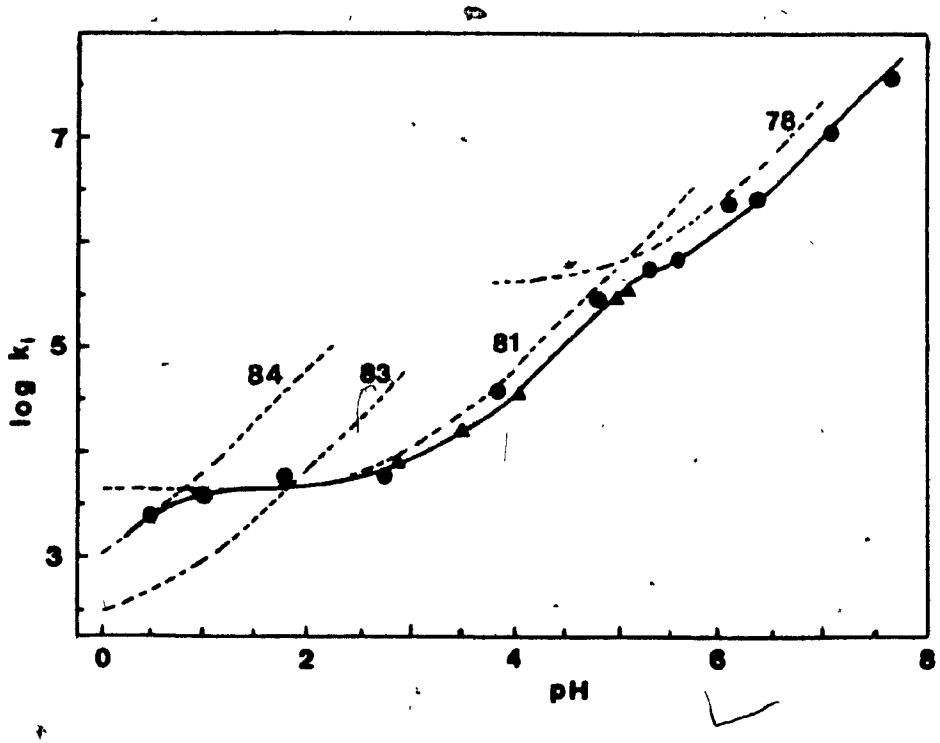


Figure 28. Broken curves are segments of rate profiles (Figure 26) for the bromination of phenol (78), 4-bromo- (81), 2,4-dibromo- (83), and 2,6-dibromophenol (84) under pseudo-first-order conditions. Full line is the rate profile for the tribromination of phenol (●) and dibromination of 4-bromophenol (▲) where $[Br_2]_o$ is in equivalent amounts to the number of brominating sites on the substrate.

The rate-limiting reaction upon phenoxide gradually disappears from the rate equation III.17 and the rate-determining step is then the mono- or dibromination of 4-bromophenol. In the range $3 < pH < 5$, this bromination is truly competitive since there is a factor of two from the value of k_2^{obsd} from equation III.16 and III.17. This fact is better illustrated in the dibromination of 4-bromophenol (points illustrated as solid triangles in Figure 28).

For pH 2-3, the rate-determining step appears to be the bromination of 4-bromophenol, as is reasonable. However, at pH < 1 the bromination of 2,6-dibromophenol seems to be rate-limiting. This is confusing since the bromination of 2,4-dibromophenol should be the rate-determining step on the basis of the rate constants obtained under pseudo-first-order conditions. In retrospect, it appears that the reactions at pH < 2 were not carried far enough (they are very slow) and so the infinity values were not very accurate.

To try to clarify the situation at low pHs computer simulations were carried out using the RMCHS program of De Tar.[121] Using the experimentally determined rate constants for the various phenols, and appropriate o/p partitioning, simulation of the tribromination of phenol at pH 1 gave the concentration profiles shown in Figure 29. These results support intuition: that the major pathway should be via 4-bromophenol and 2,4-dibromophenol. Moreover, second-order analysis of the bromination concentration values during the final one third of the reaction shows that the rate here corresponds to the bromination of 2,4-dibromophenol. To force the computer simulation to match the experimental data at pH 1 (Figure 28) one has to completely turn around the o/p ratios, therefore, to assume predominant ortho attack, in conflict with the experimentally determined o/p ratios (see above). Taken overall, we now believe that the results from the kinetic runs at pH < 2, carried out under second-order conditions, are artifacts.

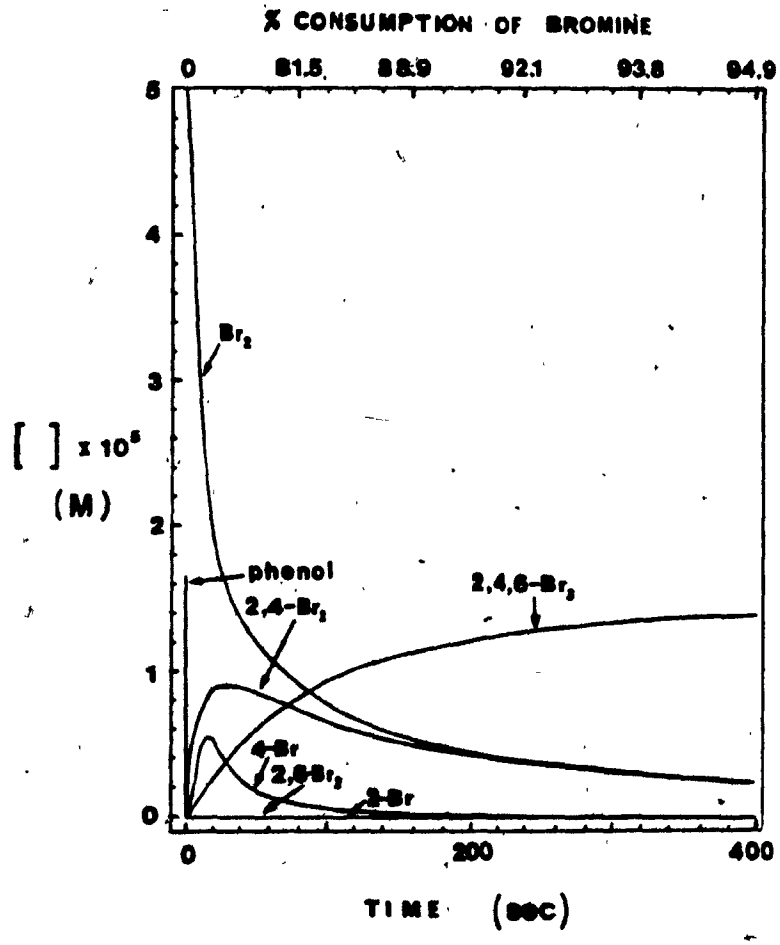


Figure 29. Concentrations of intermediates and product for the tribromination of phenol at pH 1.00 from RMCHS.[121] The values of the rate constants (Scheme X) $(k_1 + k_2)$, k_3, $(k_4 + k_5)$, k_6, and k_7 employed in this simulation are 133000, 7740, 2240, 871, 6020 M^{-1} sec^{-1} respectively, where $k_1/k_2 = 50$ and $k_4/k_5 = 50$. Analysis of $1/[Br_2] - 1/[Br_2]_o = k_2^{obsd}\, t$ yielded $k_2^{obsd} = 894$ M^{-1} sec^{-1} (c-c 0.99994).

In the preceding simulation no account was taken of the formation of intermediate bromocyclohexadienones.[95] When one cyclohexadienone intermediate per step in Scheme X is introduced in the simulation, little change was observed in the concentration profile because the lifetimes of the dienones (the longest half-life was 46 msec for

4-bromo-2,5-cyclohexadienone[95]) is much shorter than the time scale for tribromination. Thus, the bromination process can be described by considering one rather than a sequence of steps for each process in Scheme X.

Mechanism

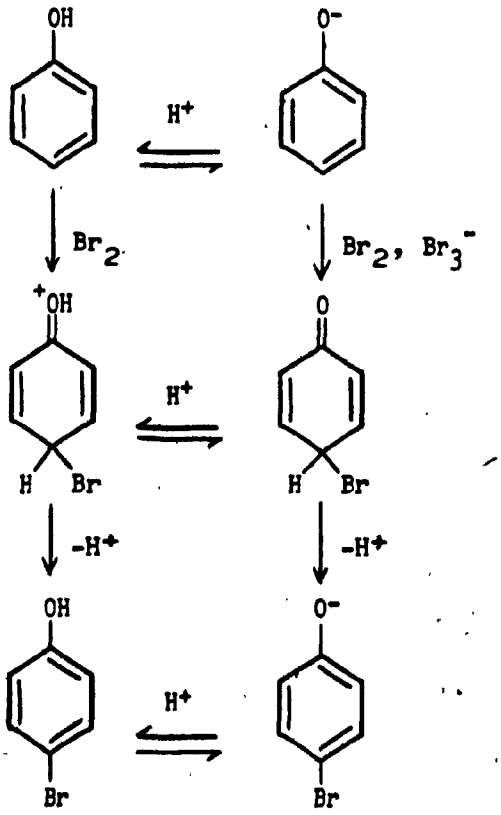
Substrate dependence studies in Table XXX corroborate the bromination of phenols to be second order. Additionally, very good second-order analyses were obtained for the dibromination of 4-bromophenol and tribromination of phenol over a wide range of pH.

In the mechanism of bromination of phenol there is participation of both Br_2 and Br_3^- in the bromination of its anion as was briefly shown above. No tribromide ion reaction was found at high acidity.[53] The rate profiles suggest the reactivity of the free-acid form of phenol (78) over the range where the slope is zero and phenoxide ion (79) where the slope is one. The predominant p-bromophenol arises from the intermediate 74 recently observed by Iyengar and Tee in this laboratory.[95] Ortho dienones were not observed; they apparently decompose too rapidly.[95] However, an analogous scheme (as Scheme XI) involving their participation may be drawn to account for the percentage of 2-bromophenol in the reaction.

The mechanism in Scheme XI is simplified by showing monobromination only. Dibromination and tribromination pathways are very similar to the bromination of the 2,4- and 2,6-dibromophenol. Also for these isomers it is difficult to dispute the intermediacy of both ortho and para

dienones, by analogy to the work of Iyengar and Tee. Scheme XI best represents our present knowledge of the bromination pathway for phenol.

Scheme XI. Mechanism of Bromination of Phenol.



Summary

Bromination product studies for phenol reported above are very similar to those reported from radiobromination.[106] The ortho/para isomer ratio increases from 0.23 to 2.1 in the range 1 < pH < 11. This effect has hitherto not been discussed or dissected especially when

correlating data using Hammett plots. In the next chapter this effect will be analyzed by applying partial rate factors for which a product study is essential.

Bell and Rawlinson[53] and Kulic and Vecera[122] have reported some diffusion rates for some para substituted phenoxides.

Kulic and Vecera[122] show that Bell's results are uncorrelated by their Hammett σ_m plot and that their results, obtained from the half-life of the reaction, are reasonably well-correlated. However, only an estimated ρ ($\sim$-3.5) was obtained because of a small number of derivatives studied. In this chapter some diffusion rate constants have been obtained from stopped-flow bromination. The values for phenol and 2,6-dibromophenol were determined for the first time. These results prepare for a full discussion on the reactivities of substituted phenols in the next chapter.

However, before one may proceed with the Hammett correlations it is imperative that the rate constants refer only to monobromination. Polybromination[115] is a problem that has required obscure corrections[53] or has been ignored.[122] Treatment of the bromination reaction as a competitive-consecutive second-order process enables the monobromination rate constants to be obtained.

The participation of tribromide ion (8.5×10^8 M^{-1} sec^{-1}) in the bromination of phenoxide was also determined. However, because insufficient work was done for the participation of tribromide ion in the bromination of substituted phenols, the separation of the contribution of bromination by bromine and tribromide ion cannot be justified for the derivatives. Thus, the total contribution to the rate constant is considered for the Hammett plots.

IV. THE HAMMETT CORRELATIONS

The intention behind writing this chapter is to correlate the influence that substituents exert on the rates of reaction of the pyrimidones, pyridones, and phenols.

In 1937, Hammett[123] recognized that this influence might be assessed by studying the same type of reaction for substituted aromatic systems keeping one substituent constant and varying the other. He approached this correlation problem with the fundamental equation IV.1:

$$\log (k/k_o) = \rho(\sigma) \qquad \text{IV.1}$$

In this equation k may be a rate constant, an acid dissociation constant, a dipole moment and so on for a substituted aromatic compound relative to the similar quantity k_o for the unsubstituted compound. The symbol sigma (σ), which is a ratio of log (K/K_o) for the ionization of benzoic acids, relates to the change in quantity due to the type of substituent while rho (ρ) is a specific constant for the reaction in question (including the reaction temperature and solvent).[124]

Normally, the meta and para influence of the substituents are considered. Ortho substitution is usually not included because the proximity of the substituent to the reaction site introduces interactions which are otherwise not present for meta or para

substitution.[124] In this chapter this problem cannot be overlooked because it would exclude at least half of the substrates studied from a correlation for the bromination reaction. It was assumed that this ortho effect, which is only exerted by the -OH or the $-O^-$ groups in this study, is a constant with different magnitudes respectively.

In the case of polysubstituted substrates it is common procedure[116a,125,126] to add the effect of the substituent constants (σ) as in equation IV.2:

$$\log (k/k_o) = \rho \sum \sigma \qquad \text{IV.2}$$

For two-substituent variation, the Hammett relationship should contain an interaction parameter ρ'[125] (equation IV.3) for the two substituents X and Y.

$$\log (k_{XY}/k_{OO}) = \rho (\sigma_X + \sigma_Y) + \rho' \sigma_X \sigma_Y \qquad \text{IV.3}$$

If the substituent Y is hydrogen, for which σ is zero by definition, then equation IV.3 reduces to IV.1. If Y is kept constant but is not hydrogen then equation IV.3 reduces to:

$$\log (k_{XY}/k_{OY}) = (\rho + \rho' \sigma_Y) \sigma_X \qquad \text{IV.4}$$

Thus, even for the multiparameter situation a plot of log (k_{XY}/k_{OY}) versus σ_X or $\sum \sigma_{Xi}$, should yield a straight line if the Hammett relationship is obeyed. Also calculations of ρ are invariant whether log k_{XY} or the ratio log (k_{XY}/k_{OY}) is plotted. In this chapter the former method is adopted without regard to a reference substrate: one where $\sum \sigma_{Xi} = 0$.

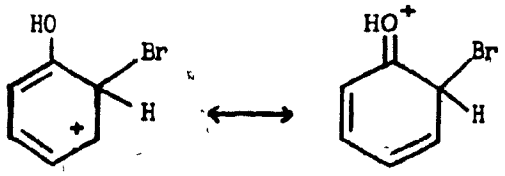
Equation IV.2 is an approach to a linear free energy

relationship[124-126] since it contains the logarithm of k which is directly proportional to G. It implies that addition of a substituent to a molecule is similar to adding an extra G term for the new interaction and subtracting G for the interaction for the previous substituent. Extention of this theory leads to the breakdown of the individual interactions in a molecule;[125]

$$G_{YA} = G_{YA}^{\text{bonding}} + G_{YA}^{\text{polar}} + G_{YA}^{\text{resonance}} + G_{YA}^{\text{steric}} \qquad \text{IV.5}$$

This breakdown is directly related to the refinements of σ since Hammett's introduction of the constant.

For example, to overcome the deviations of strong electron-withdrawing and electron-donating groups in the para position vis-a-vis equation IV.2 sigma minus (σ^-) and sigma plus (σ^+) were devised, respectively. Sigma plus was assigned relative to the solvolysis of 2-chloro-2-phenylpropane, where $\sum \sigma_i^+ = 0$. For some meta substituents, σ^+ have been measured, but they do not differ appreciably from σ_m values, as originally defined.[124] This is because no strong resonance or electronic effect can be exerted in a meta position by any substituent. This new constant parameter (σ^+) is useful in explaining electrophilic reactions such as bromination reactions where there is strong stabilization (as can be seen from structures 87 and 88) by the electron-releasing groups ortho or para to the site of attack.



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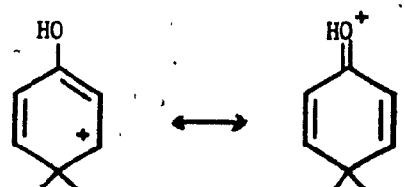

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In this chapter σ^+ will be employed, where known, otherwise sigma meta (σ_m) will be employed for a substituent.

Partial Rate Constants

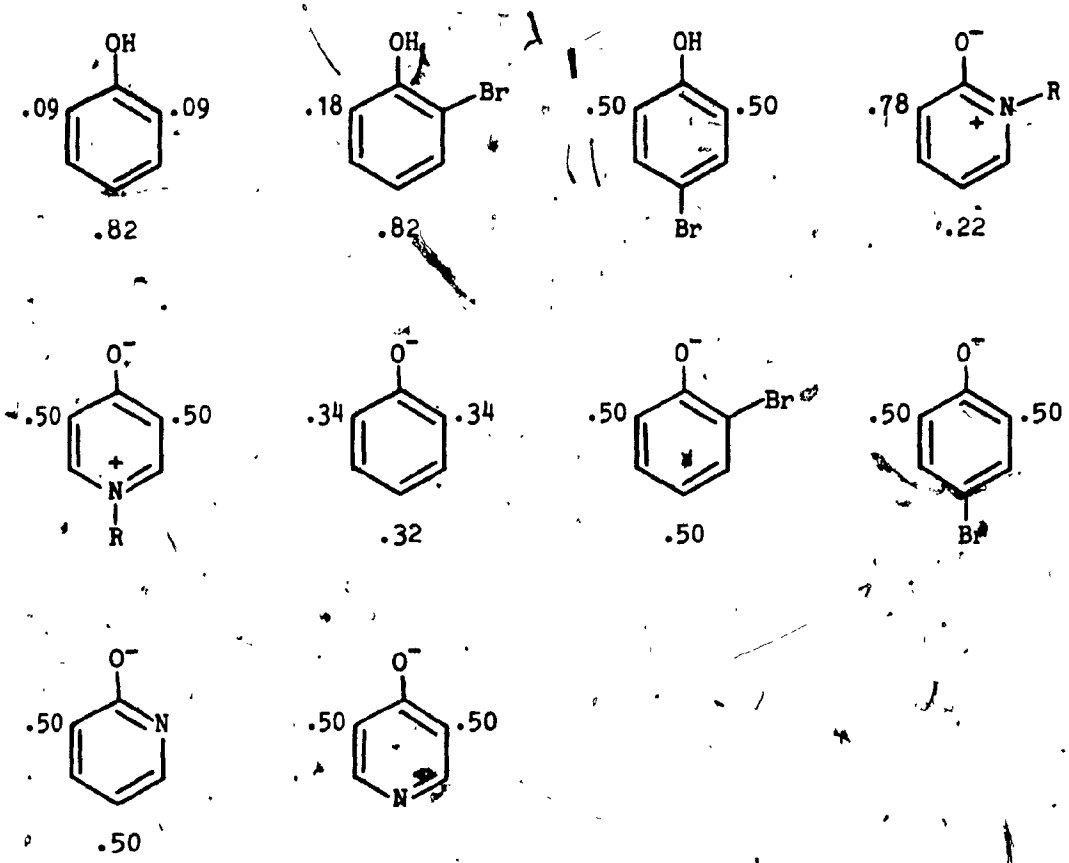
Partial rate constants are a measure of intramolecular selectivity. Measurements of isomeric product ratios indicate how, for instance, in electrophilic substitution the reagent interacts with a given substrate by changes of activation energy at the two different sites. Calculations of the partial rates may not necessarily involve measurements of rate constants[124] but may be obtained by product ratios for a competitive reaction.

Defining k_p, k_m, k_o as the partial rates of para, meta, and ortho attack of bromine on phenols* (and heteroaromatic phenols) their calculation may be done by multiplying the total rate constant by the probability constant for attack of bromine at the site in question. The percent probability constants have been shown for phenol on page 145, and can be calculated from isomeric product ratios. Listed below are the values employed for the correlations to follow.**

---

* As mentioned above the substrate to which the partial rate should be compared (i.e. $\sum \sigma_i^+ = 0$) is neglected.

** Since there is no meta bromination, the probability factor meta to -OH or $-O^-$ group is zero. On the other hand, those for disubstituted substrates (one reaction site) are assigned a probability of one.



Using these probability factors and total rate constants one calculates <u>partial</u> rate constants which are statistically corrected for the number of equivalent reactive sites. Since bromination is an electrophilic substitution, they should vary with (σ^+)[127,128] according to equations IV.6 and IV.7 where C_r refers to the logarithm of the rate constant for the reference substrate:

$$\log k_p = \rho(\sigma_p^+)_{OH} + \rho\sum\{\sigma_m^+\} + C_r \qquad \text{IV.6}$$

$$\log k_o = \rho(\sigma_o^+)_{OH} + \rho\sum\{\sigma_m^+\} + C_r \qquad \text{IV.7}$$

Perhaps the more important relationship that can be shown for partial rate constants[126] is that of equation IV.8:

$$\Delta(\Delta G^\ddagger) = \Delta G^\ddagger \text{ para} - \Delta G^\ddagger \text{ ortho} = -RT \ln (k_p/k_o) \qquad \text{IV.8}$$

Thus, the ratio k_p/k_o measures the difference in free-energy change of the activated states of para and ortho attack of bromine on phenol (in general the substrate).

To present the results of the kinetics of bromination, some sigma constants are needed. Those which were employed in the correlations are listed in Table XXXIV. The σ_o^+ constants are not listed in the literature, but, as previously mentioned, they are important. The value for a hydroxy substituent was estimated from equations IV.6 and IV.7 for phenol and bromophenols. Subsequently, it was readjusted to give the best correlation line in Figure 30.

Table XXXIV. Sigma Meta and Sigma Plus Employed in Correlation of Partial Rate Constants.

Substituent	(σ_m)[129]	(σ_m^+)[126]	σ_p^+
H[a]	0.00	0.00	0.00
CH_3	−0.06 ± 0.03	−0.07	
CO_2H	0.35 ± 0.18	0.32	
COO^-	0.09 (−0.19)	−0.028	
CO_2Me	0.35 ± 0.10	0.37	
CO_2Et	0.35 ± 0.10	0.37	
NO_2	0.71 ± 0.04	0.68	
OMe	0.10 ± 0.03	0.047	−0.78[125,126]
SO_2Me	0.68 ± 0.10	0.68	
OH	0.02 ± 0.08		−0.92[126,129]
(O^-)[b]	−0.71		−2.3[125,129]
Br	0.37 ± 0.04	0.41	
Cl	0.37 ± 0.04	0.40	
-N=	0.68 ± 0.06	0.55[c,94] (0.57)[129]	
$=\overset{+}{N}H$	2.21 ± 0.16	2.05[c,94]	
$=\overset{+}{N}CH_3$		1.98[d,94]	

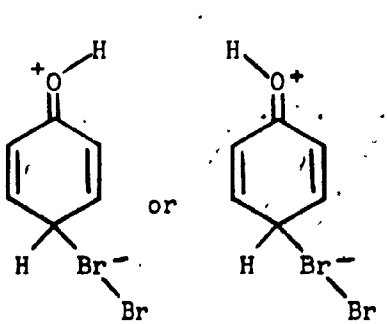
[a] By definition.
[b] Value for charged species is not very accurate.[129]
[c] An average value.
[d] Estimated assuming an activating effect of 0.07 for methyl group.

Correlations for Phenols

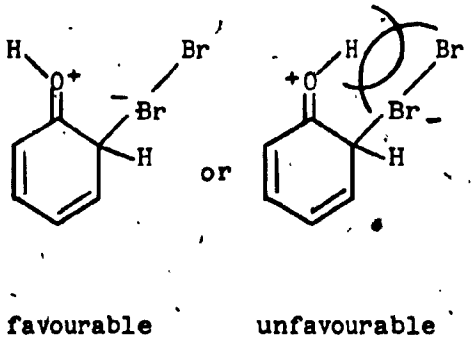
The list of partial rates for the bromination of phenols is reproduced in Table XXXV. Figure 30 correlates the bromination rates of undissociated phenols. This figure clearly shows that the partial rates are linear with $\sum\sigma^+$. The values of $\sigma_o^+ = -0.76$ and of $\sigma_p^+ = -0.92$ for hydroxyl substituent correlate all the phenols studied with a $\rho^+ = -3.29$ (c-c -.993).

The significance behind Figure 30 is that most likely a unique mechanism applies for the ortho or para bromination in acidic medium. Apparently ipso attack,[95] if it occurs, does not partake to any large extent in the mode of reaction. Otherwise, some deviations from the line would have been seen, especially for 4-bromo and 2,4-dibromophenol. For these a smaller magnitude of the partial rate constant for ortho bromination would have been expected.

Application of equation IV.8 gives $\Delta(\Delta G^{\ddagger})p/o = -0.94$ Kcal/mol for phenol. This is a sizeable rate retardation exerted by the hydroxyl group in the ortho position. This is in part due to an increased $\Delta S^{\ddagger}$ for ortho attack of the bromine molecule which requires an E arrangement of the acidic hydrogen.



both likely



favourable unfavourable

This high energy arrangement decreases as the ratio of ionized phenol increases. Thus, at pH = 7.5 $\Delta(\Delta G^{\ddagger})p/o$ = -0.47 Kcal/mol, and at pH = 10 (completely ionized) $\Delta(\Delta G^{\ddagger})p/o$ = 0.036 Kcal/mol. For the completely ionized phenol then, ortho and para bromination is equally likely.

Table XXXV. Partial Rates for Bromination of Phenols and Phenoxides at Positions Ortho and Para.

Phenol	Neutral k_{total} $M^{-1}sec^{-1}$	k_o $M^{-1}sec^{-1}$	k_p $M^{-1}sec^{-1}$	Anion k_{total} X 10^{-9} $M^{-1}sec^{-1}$	k_o X 10^{-9} $M^{-1}sec^{-1}$	k_p X 10^{-9} $M^{-1}sec^{-1}$
H	410000	741000	365000	10.5[a]	3.57	3.36
2-Br	15000	28500	12200	5.5[a]	2.75	2.75
4-Br	4400	2200		7.0[a]	3.5	
2,4-diBr	240	240		4.2	4.2	
2,6-diBr	500		500	2.8		2.8

[a] The total rate was corrected for polybromination by inference to the consecutive-second-order rate constants obtained (see Figure 28).

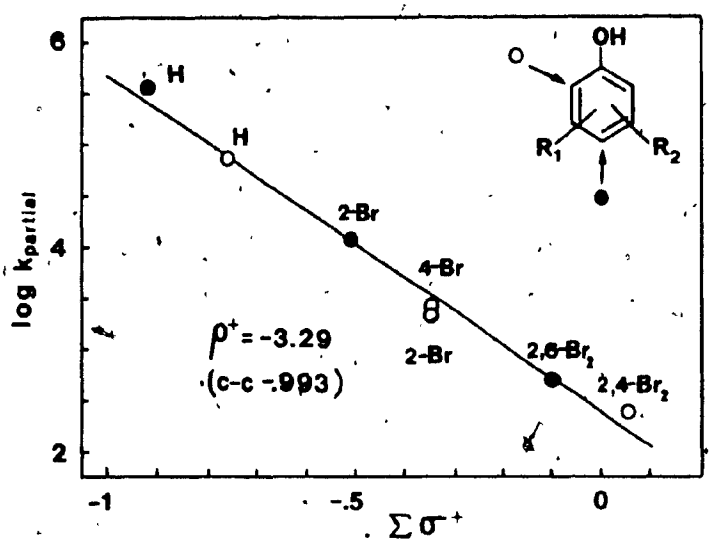


Figure 30. Correlation of partial rates (log $k_{partial}$) versus $\Sigma\sigma^+$ for bromination ortho (O) and para (●) to phenols: ($\sigma_o^+)_{OH}$ = -0.76 and ($\sigma_p^+)_{OH}$ = -0.92.

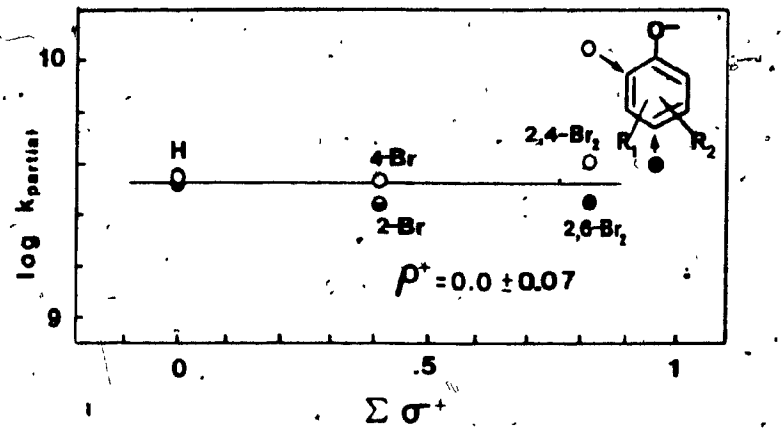


Figure 31. Correlation of partial rates (log $k_{partial}$) versus $\Sigma\sigma^+$ for bromination ortho (O) and para (●) to phenoxides. The reference substrate was assumed to be the phenoxide ion.

Anionic bromination of phenols was correlated with $\Sigma\sigma_i^+$, as in Figure 31. The slope (ρ = 0!) indicates that the substituents no longer have any effect upon reactivity. Thus, the diffusion-controlled limit of the reaction has been reached apparently at $(3.4 + 0.6) \times 10^9$ M^{-1} $sec.^{-1}$ The predicted diffusion rate[97] 7.4×10^9 M^{-1} s^{-1} is then about twice bigger than that witnessed in these experiments. This factor may possibly be explainable in the light of the kinetic equations developed by Simmons.[103,130]

For the process below P* is the fraction of the initial diffusion-controlled encounters which give $(AB)^1$, and k_D the overall rate constant for the formation of the encounter complex.

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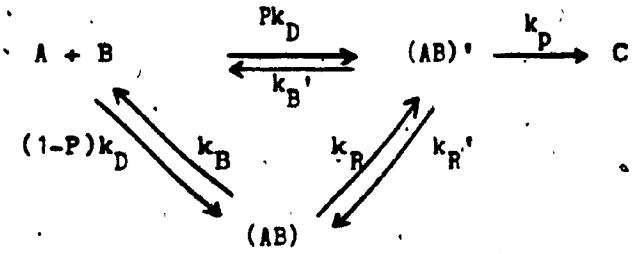
* P is termed a geometric factor. The rate constant k_p can be expressed as $\gamma\nu$ where ν is the collision frequency and γ is the probability of reaction per correctly oriented collision.[103]



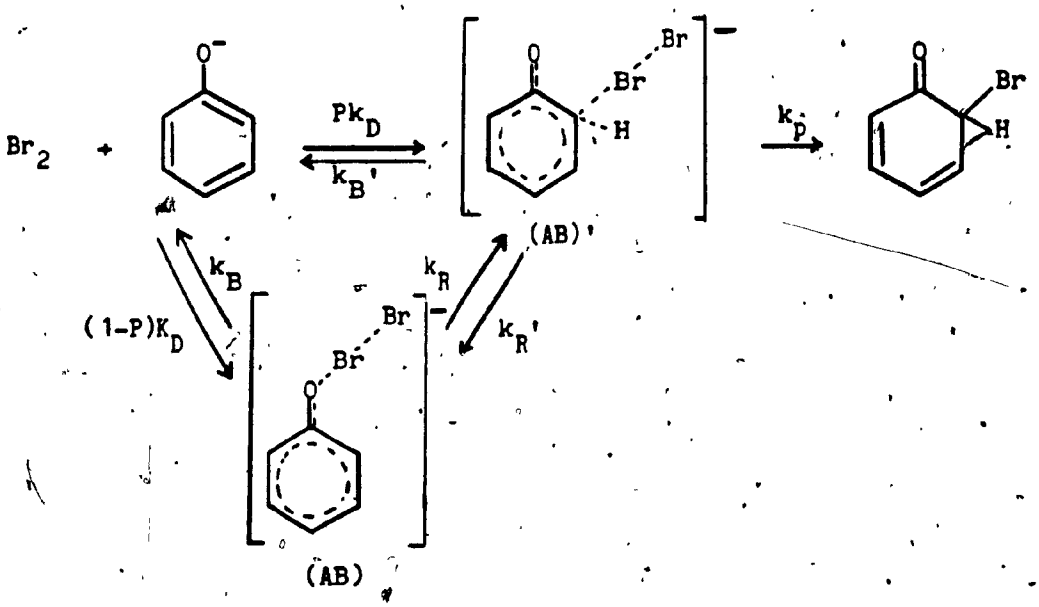
The forward rate constant k_f may be expressed[103] as:

$$k_f = \frac{k_D k_p (Pk_B + k_R)}{k_B (k_R + k_B' + k_p) + k_R (k_B' + k_p)} \qquad \text{IV.9}$$

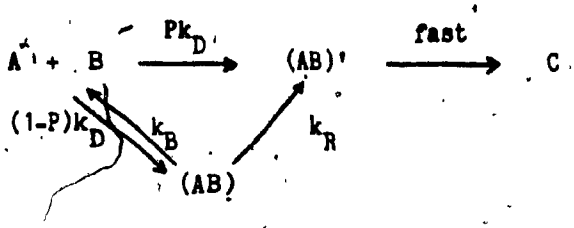
when there is no orientational preference of the two reactants (P = 1) so (AB) and (AB') are indistinguishable and equation IV.9 reduces to IV.10:

$$k_f = \frac{k_D k_p}{(k_B' + k_p)} \qquad \text{IV.10}$$

In the bromination of phenols the process referred to above may have the following significance:



In the event that complex (AB)' and (AB) are both of equal likelihood, then the apparent rate constant is given by equation IV.10. More likely is the case where $P < 1$ and $k_p >> k_R'$, $k_p >> k_B'$. This refers to a process of the type:



Equation IV.9 reduces to:

$$k_f = k_D(Pk_B + k_R')/(k_B + k_R') \qquad \text{IV.11}$$

This last equation can be fragmented further. Consider the subcase where $k_R >> k_B$, $k_R' >> Pk_B$ then:

$$k_f = k_D \qquad \text{IV.12}$$

This equation signifies that the apparent diffusion rate should be equivalent to the predicted diffusion rate. But, as discussed above, this situation does not appear to be the case since our observed value of 3×10^9 M^{-1} sec^{-1} is lower than the predicted 7.4×10^9 M^{-1} $sec.^{-1}$

Consider then the subcase where $k_B >> k_R$ but $k_R >> Pk_B$ $(P << 1)$. The mechanism under these conditions reduces to:

$$A + B \underset{k_B}{\overset{k_D}{\rightleftharpoons}} (AB) \xrightarrow{k_R} (AB)' \xrightarrow{\text{fast}} C$$

Equation IV.11 simplifies to:

$$k_f = k_D k_R / k_B \qquad \text{IV.13}$$

This question corresponds to a reaction which is not even close to diffusion controlled. This does not appear to be the case for phenoxide ions.

The alternative situation, a melange of the last two subcases, appears more acceptable in this context. This case arises from considering $k_B \gg k_R$, $Pk_B \gg k_R$, where equation IV.11 reduces to:

$$k_f = Pk_D \qquad \text{IV.14}$$

This equation, if applicable, assumes that the geometric factor P for bromination of phenoxides has a value of ~0.5.

In summary, it is theoretically plausible for a diffusion controlled rate, denoted by $\rho = 0$, to be less than that predicted by simple collision theory if geometric factors are important.[103,130]

The Pyridones and Pyrimidones

Prior to the present work knowledge on these systems was limited. In the discussion of the mechanism of bromination of these substrates it was concluded that, depending on the pH, the reaction occurred on both the free-acid and anions. This was deduced by contrasting the rate constants of suitable model derivatives for each form. Analogy of the rate profiles, in a few cases, aided in this research.

This chapter deals with the quantification of the effect of the ring-nitrogen in the bromination reaction and the nature of the reactive

species. The rate of reaction for a heterocyclic phenol is compared with phenols. The Hammett equation will be used where sigma plus constants are assigned to each heterogroup: =N-, $\geq N^{\pm}H$, $\geq N^{\pm}CH_3$, and a single ρ^+ value for the bromination reaction.

Again the problem is two-fold. How to deal with and separate ortho and para reactivities and then to correlate all the data in terms of the substituent -OH or $-O^-$ as the case may be. Partial rate factors should solve the first problem, while the correlation with phenols and phenoxides should at least serve as a probe for the second problem.

Acheson[93] assumed that the pyridones have a major contribution from their dipolar valence-bond forms. Thus, the neutral form of the pyridone, and by analogy the pyrimidones also, contain an azonium-nitrogen $\geq N^{\pm}R$ (R = H, CH_3) for which Tomasik and Johnson[94] have assigned values of $\sigma_m = \sigma_m^+$ of 2.05 and 1.98 for hydrogen and methyl groups respectively. The anionic form contains the aza-nitrogen whose average sigma value, employed in this chapter, was 0.55.

In the dipolar forms, these heterocycles may be related to phenoxides, because of the common $-O^-$ substituent; however, they are neutral. This, on the other hand, suggests that the comparison should be with the neutral forms of the phenols. Combination of these two criteria necessitates contrast of both phenols and phenoxides with pyridones, pyrimidones, and their anions. The way to achieve this objective, and establish a unique ρ^+ value for bromination of these phenolic systems, is to assign a σ_o^+ and σ_p^+ values for $-O^-$ relative to that for -OH estimated above.

Table XXXVI gives the partial rate constants for bromination of the pyridones and pyrimidones via their neutral and anionic forms. Only

partial rate constants below 1 X 10^8 $M^{-1}sec^{-1}$ (a gap appears to exist in this plot between 10^8 - 10^9 M^{-1} sec^{-1}) were plotted in Figure 32. The best correlation line was achieved when σ_o^+ = -2.54 and σ_p^+ = -2.59 for $-O^-$ substituent.[a] This shows clearly that the 4-pyrimidones, 1-methyl-2-pyridone, and 2-pyridone deviate considerably. In fact, when they are removed from the correlation it is found that ρ^+ = -3.41 with an acceptable correlation coefficient of 0.993 and an intercept value of 2.41.

Thus, pyridones and pyrimidones can be treated as neutral phenols and deactivated pyridones and pyrimidones. Aside from the exception outlined above, showing ortho[b] reactivity, this plot demonstrates the similar mechanistic pathway exhibited by the different compounds. It was already pointed out in Chapter II that the deviation for 2-pyridone and its N-methyl derivative, may have been due to complexation prior to bromination. The Hammett plot is further evidence of their abnormal behaviour.

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[a] An estimated value of σ_p^+ for $-O^-M^+$ was found to be -2.3 (see Table XXXIV).

[b] σ_o^+ usually correlate poorly!

Table XXXVI. Partial Rates for Bromination of Neutral and Anionic Forms of Pyridones and Pyrimidones.

Compound	Form of the Substrate: Neutral k_{total} $M^{-1}sec^{-1}$	Neutral k_o $M^{-1}sec^{-1}$	Neutral k_p $M^{-1}sec^{-1}$	Anionic k_{total} $\times 10^{-9}$ $M^{-1}sec^{-1}$	Anionic k_o $\times 10^{-8}$ $M^{-1}sec^{-1}$	Anionic k_p $\times 10^{-8}$ $M^{-1}sec^{-1}$
2-Pyridone	22000	17200	4840	1.5[a]	7.5	7.5
1-Me __	47000	36700	1030			
3-Br __	1650		1650	0.60		6.0
1-Me-3-Br __	2720		2720			
5-Br __	380	380		0.49	4.9	
1-Me-5-Br __	760	760				
4-Pyridone	7300	3500		1.35[a]	6.75	
1-Me __	12800	6400				
3-Br __	650	650		0.082	0.828	
1-Me-3-Br __	549	549				
2-Pyrimidone	~250	~250		0.051		0.51
1-Me __	250		250			
4-Pyrimidone	~11	~11		0.011	0.11	
1-Me __	15	15				
3-Me __	8.5	8.5				

[a] The total bromination rate was corrected for dibromination (see Figures 23 and 24).

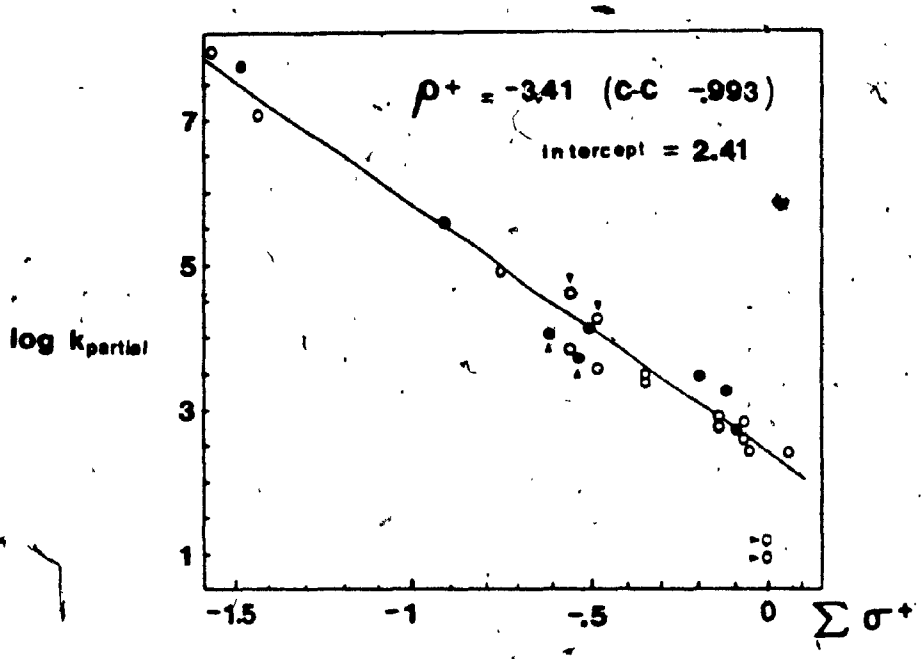


Figure 32. Plot of partial rates (log $k_{partial}$) at sites ortho (O) and para (●) to phenols and heteroaromatic phenols versus $\Sigma\sigma^+$. Note that points for N-methyl-4-pyrimidones, N-methyl and 2-pyridone (shown by arrowheads) were left out of the correlation. The deviations for 2-pyridones may be due to the predominant ortho bromination although there is the choice of ortho or para substitution. Differences for N-methyl-4-pyrimidones are: (1) I = 0.11 M at 30°C rather than I = 1.01 M at 25°C, (2) large positive salts effects, (3) buffer catalysis. Points taken from Table XXXVI.

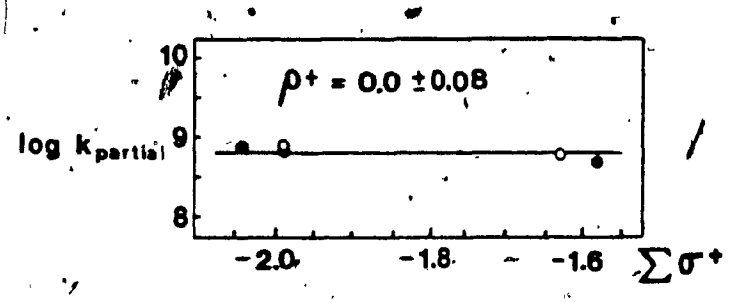
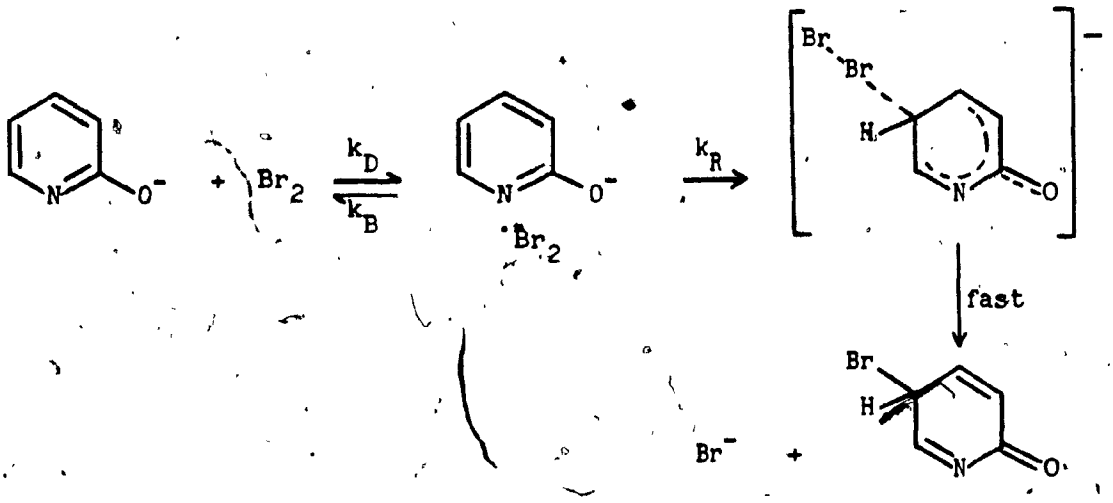


Figure 33. Plot of partial rates (log $k_{partial}$) at sites ortho (O) and para (●) to 2- and 4-pyridoxides (except 3-bromo-4-pyridoxide is plotted in Figure 32) versus $\Sigma\sigma^+$. The values $(\sigma_o^+)_{O^-}$ and $(\sigma_p^+)_{O^-}$ obtained in the correlation of Figure 32 were employed. The intercept value is 8.81 ± 0.08.

A correlation of the anionic bromination was done for the pyridones. Using σ_o^+ and σ_p^+ estimated above, the partial bromination rates for these systems are plotted in Figure 33. Within experimental error it can be said that $\rho^+ = 0$ and therefore the process is diffusion controlled with a low diffusion rate constant of 6.5×10^8 M^{-1} $sec.^{-1}$

The explanation of this low value is rather simple if the pathway outlined by equation IV.13[103] is assumed to be operational. In chemical jargon this equation implies that a stable complex of bromine is formed with the pyridoxides at a site away from the reactive site which rearranges to a reactive complex:



Assuming the theoretical diffusion value to be 7.4×10^9 M^{-1} $sec.^{-1}$ then the constant k_R/k_B for the pyridones can be estimated at 0.087.

To elucidate the scope of the Hammett relationship, as dissected in this chapter, all the partial bromination rates for different phenols, collected in Table XXXVII, were plotted together with the rate constants obtained in this in this study versus $\sum \sigma^+$ in Figure 34. This clearly shows the breakdown of the reactivity trend for neutral and deactivated anions close to the diffusion-controlled region (see below).

Table XXXVII. Compilation of Partial Rate Constants for Bromination of Phenols and Phenoxides from the Literature.[53,105,122]

Substituent on Phenol	Phenolic -OH Group: Neutral k_{total} X 10^{-3} $M^{-1}sec^{-1}$	Neutral k_o X 10^{-3} $M^{-1}sec^{-1}$	Neutral k_p X 10^{-3} $M^{-1}sec^{-1}$	Anionic k_{total} X 10^{-9} $M^{-1}sec^{-1}$	Anionic k_o X 10^{-9} $M^{-1}sec^{-1}$
4-NO_2	0.11	0.055		0.805[a]	0.402
4-CH_3SO_2	0.15	0.075		2.0[a]	1.0
4-Cl	3.25	1.62		10.4[a]	5.2
4-CH_3	453	226			
2,6-diCH_3	7.4		7.4		
2-CH_3	780	140	640		
4-COOH	3.60	1.80			
4-COO^-	1530	766			
4-COOEt	2.50	1.25		4.47[a]	2.24
2-COO^-	1160	209	955		

[a] The literature rate was corrected for dibromination, by contrast with 4-bromophenol, by dividing it by two.

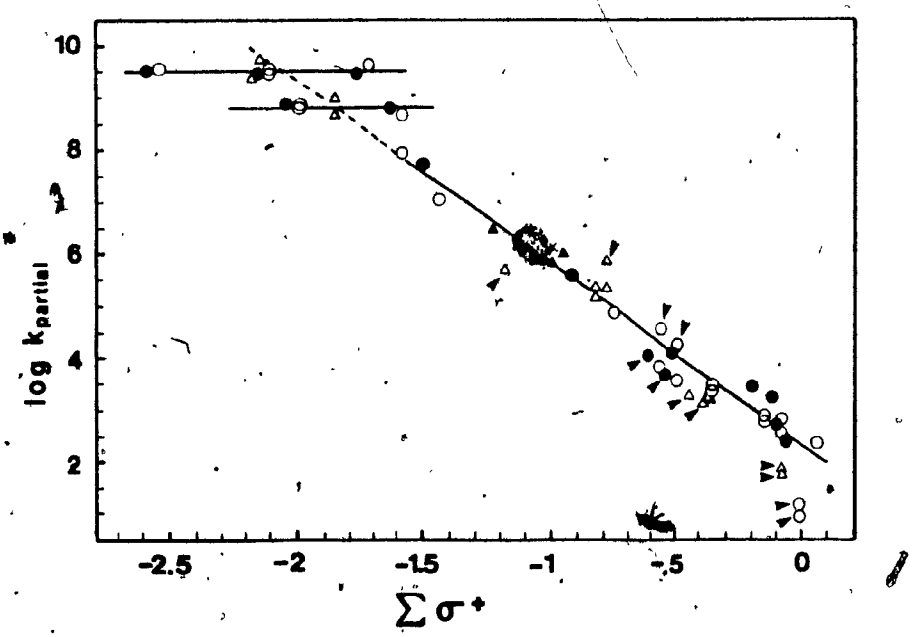


Figure 34. Plots of partial rates (log $k_{partial}$) versus $\sum \sigma^+$ for bromination ortho (O , Δ) and para (● , ▲) to aromatic and heteroaromatic phenols and phenoxides from this work (O , ●) and from the literature (Δ , ▲).[53,105,122] The slope of the solid line ρ^+ = -3.43 (c-c -.985) and intercept 2.33 were obtained using the same sigma constants as described for Figure 32. Points with arrowheads were omitted from this correlation.

That a similar ρ^+ value is to be expected for ortho and para bromination can be inferred from the work of Dubois et al. on the bromination of anisole.[116a] His depicted correlation line for para bromination of anisoles gives a ρ^+ = -6.4[a] ± 0.28 while that for ortho bromination gives ρ^+ = -6.54 ± 0.3.

This concept, that the ρ^+ value should be unique, was extended for

[a] Dubois[116a] reports a ρ^+ = -5.56 which is incorrect for the depicted line in Graph A of Figure 5.

the $-O^-$ substituent giving σ_o^+ and σ_p^+ values -2.54 and -2.59 respectively. These two values are closer to each other compared to those for the hydroxy substituent indicating strong similarity between resonance, vibrational, and inductive effects for substituents ortho to $-O.^-$

In summary, using $\sigma^+ = 0.55$ for aza-nitrogen,[94] a value of 2.05 for azonium nitrogen,[94] and the appropriate partial rate constants taken from different literature sources, a $\rho^+ = -3.43$ was calculated. This value is similar to the estimate of -3.5 by Kulic and Vecera.[122] Their value is fortuitous since they have correlated points in the diffusion-controlled limit (dotted line in Figure 34) and spanning a small range of reactivity (one power of ten), whereas the plot in Figure 34 depicts values covering seven powers of ten. Their value is also fortuitous for the reason that they employ the total rate constant. Taken overall the values in Tables XXXV and XXXVI support the notion that the pyridones and pyrimidones, reacting via their free-base, are behaving as substituted phenoxide ions.

Substrates, not capable of reacting as substituted phenoxides, such as 2-methoxypyridine, have reactivities appropriate for anisoles. For anisole itself $k_p = (2.98 \times 10^4\ M^{-1}\ sec^{-1})$,[116a] and $\rho^+ = -6.4$ for para bromination. From these values and $\sigma^+ = 0.55$ for aza-nitrogen,[94] a value of $k_p = 9.0\ M^{-1}\ sec^{-1}$ for 2-methoxypyridine is obtained, in excellent agreement with the observed value of $9.5\ M^{-1}\ sec^{-1}$ (see Table XXI page 110). For ortho substitution in anisole $k_o = 708\ M^{-1}\ sec.^{-1}$ $\rho^+ = -6.54$,[116a] and taking the same sigma plus value for aza-nitrogen, gives an expected value for the bromination constant for 4-methoxypyridine of $0.18\ M^{-1}\ sec.^{-1}$ However, the insolubility of the

bromine complex formed in water has precluded the determination of the bromination rate constant for this substrate.

V. EXPERIMENTAL

Materials

The melting points give below are uncorrected. Elemental analyses were performed by Galbraith Labs. Inc., Knoxville, Tennessee.

The following compounds were of commercial source: phenol (Macco reagent), 2-bromophenol (Pfaltz and Bauer, Inc.) contains traces of phenol as determined by gas chromatography, and 2-methoxypyridine (Aldrich) were used without further purification. 2,4-Dibromophenol (Eastman Organic Chemicals), was recrystallized from carbon tetrachloride/petroleum ether 30-60°C and 4-bromophenol (Pfaltz and Bauer, Inc.) was recrystallized from light petroleum.

The following compounds were obtained by established literature procedures: 4-pyrimidone,[131] 1,4-(3,4)dihydro-1,3-dimethyl-4-oxo-pyrimidinium iodide and perchlorate.[18c] 2-Pyrimidone and 1-methyl-2-oxo-pyrimidinium bromide were obtained by cyclization of urea and N-methylurea with malonaldehyde tetramethyl diacetal (Aldrich) according to literature procedures[132,133] for the hydrochlorides but using hydrobromic acid in place of hydrochloric acid.

3-Aminopyridine (Aldrich) was diazotized to 3-bromopyridine,[141]

oxidized to 3-bromopyridine-N-oxide[136] which rearranges to 3-bromo-2-pyridone by reaction with acetic anhydride and hydrolysis.[137] 5-Bromo-2-pyridone was prepared from the bromination of 2-aminopyridine (Aldrich) to 2-amino-5-bromopyridine[138] followed by a diazotization.[139]

2,6-Dibromophenol was obtained from decarboxylation of 3,5-dibromo-4-hydroxybenzoic acid.[140]

1-Methyl-4-oxo-pyrimidinium Bromide:

4-Pyrimidone (10.0 g, 0.104 mol) and potassium hydroxide (7.0 g, 0.12 mol) were dissolved in 200 mL of methanol. To this stirred solution was slowly added (14 g, 0.11 mol) of dimethyl sulfate dissolved in 40 mL of methanol. When addition was complete, the mixture was heated for 15 min and basified. Precipitation of the salts was completed by cooling and the addition of acetone. These were filtered off and the solvent was evaporated. This process was repeated twice with addition of acetone/chloroform (1:1). The salt-free residue was extacted several times with small portions of boiling benzene. The final solution of benzene was 300 mL.

The benzene-insoluble residue was dissolved in acetone and treated with slight excess of hydrobromic acid. After cooling overnight, the crude 1-methyl-4-oxo-pyridinium bromide amounted to 4.54 g (22.8%). Recrystallization from ethanol gave a compound mp 202-203°C. The NMR and IR spectra of its free base agreed with the literature.[31]

3-Methyl-4-oxo-pyrimidinium Bromide:

The benzene-soluble material, from the methylation of 4-pyrimidone, was recrystallized from benzene giving the appropriate spectra[31] (this material yellows after several weeks). The crystals, dissolved in acetone, were treated with hydrobromic acid, as above, yielding 7.54 g (38%) of the title compound mp 216-8°C from ethanol.

Reaction of 4- and 2-Pyrimidone with Bromine

5-Bromo-4-oxo-pyrimidine:

Bromine (1.58 g, 0.0100 mol) in 0.1 M potassium bromide solution was added dropwise to (0.961 g, 0.0100 mol) of 4-pyrimidinone in 0.10 M potassium hydroxide solution. After addition of bromine the solution was acidified (pH 1) and evaporated. Extraction with ethanol gave the 5-bromo-4-oxo-pyrimidine 1.22 g (70%) identical from the product of the reaction in methanol.[31] The same experiment carried out under kinetic conditions and analyzed by UV spectrometry showed the product to be the 5-bromo derivative.

5-Bromo-2-oxo-pyrimidine:

Bromination, as described above for 5-bromo-4-oxo-pyrimidine, gave 78% of the title compound. The infrared was identical with a sample from Banerjee.[18c] Bromination under kinetic conditions and analyzed by UV spectrometry demonstrated that bromine occupied position 5.

Reaction of 4-Pyrimidone with Two Equivalents of Bromine

Synthesis of 38 (page 63):

To 4-pyrimidone (0.961 g, 0.100 mmol) dissolved in 10 mL of methanol was added two equivalents of bromine in methanol slowly (a faint bromine colour persisted even after boiling for five minutes at the end of the addition period). The solution was then cooled and excess bromine was destroyed by addition of a few drops of acetone. Addition of ether, ten-fold the amount of methanol, caused precipitation of a white solid. Recrystallization from acetone, acetonitrile, methanol, or water gave a white granular solid 2.10 g melting with decomposition at 151-2°C (see Figure 35). Addition of silver nitrate caused immediate precipitation of silver bromide. Mass spectrum (recorded by Dr. E. Kazdan) indicated the presence of m/e peaks > 200. ^{1}H NMR spectrum in D_2O/DSS indicated two methoxyls (distinct from an added amount of methanol). Exchangeable hydrogens were inferred from infrared spectrum (see Figure 36).

Analysis: Calculated for $C_6H_{11}N_2O_3Br_3$: C, 18.07%; H, 2.78%; N, 7.02%; O, 12.03%; Br, 60.10%.

Found: C, 18.18%; H, 2.84%; N, 7.11%; O, 12.03%; Br, 57.09%.

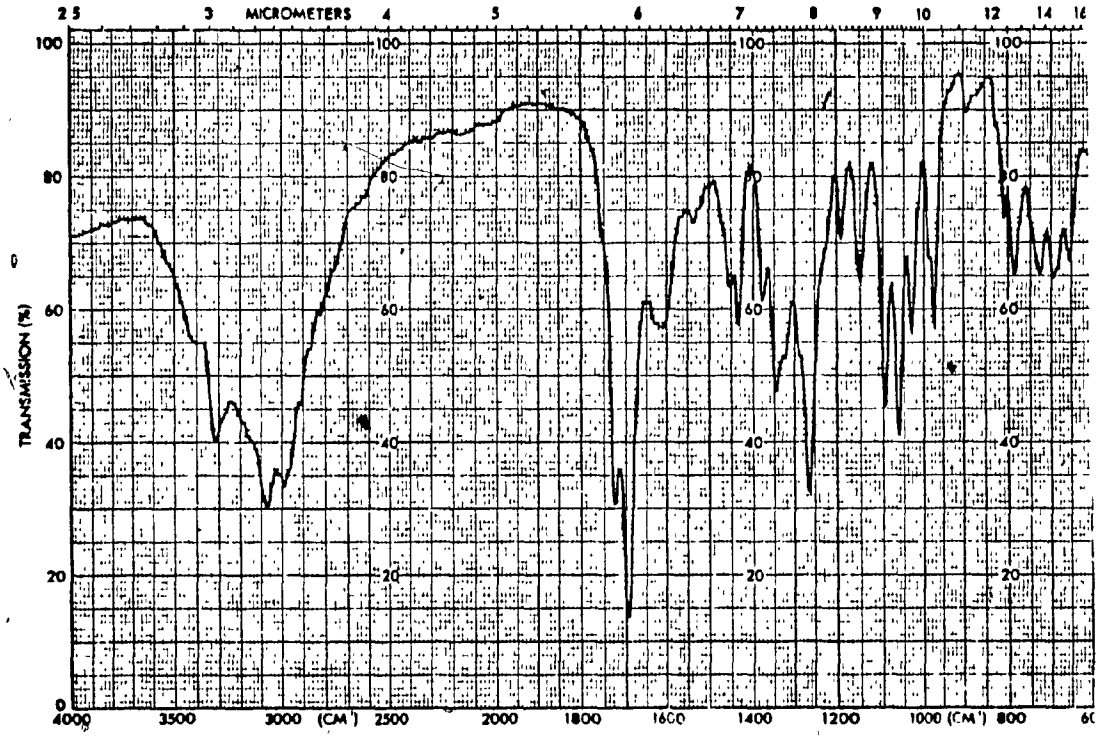


Figure 35. IR spectrum (KBr wafer) of compound 38.

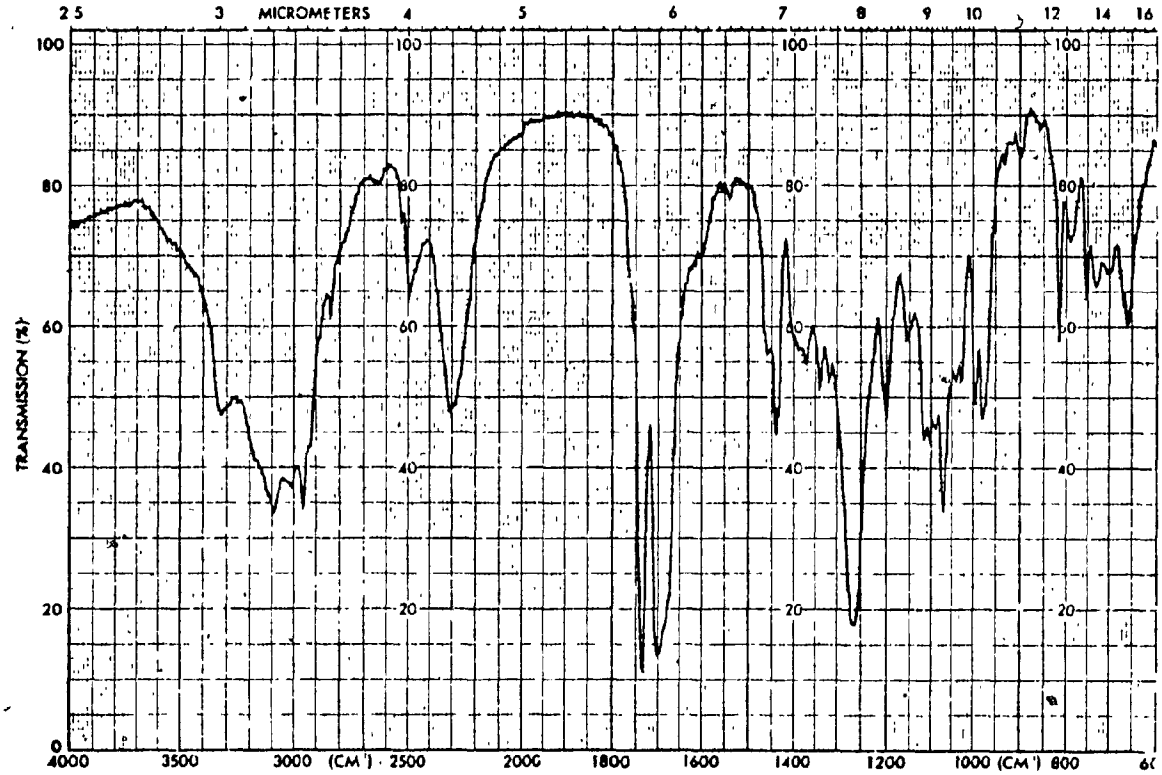


Figure 36. IR spectrum (KBr wafer) of compound 38 recrystallized from D_2O.

2-Pyridone:

This Aldrich product was recrystallized three times from petroleum ether to give long needles, mp 106-107°C (lit.[85] 106°C, after sublimation). Its sodium salt separated as plates upon addition of acetone to an ethanolic solution of equimolar amounts of 2-pyridone and sodium ethoxide. Several recrystallizations from ethanol gave a hydrate,*,[85] mp 165-167°C. Proton NMR indicated approximately two waters of crystallization. Elemental analysis was not particularly good.

Analysis: Calculated for $C_5H_4NONa \cdot 2H_2O$: C, 39.22%; H, 5.27%; N, 9.14%. Found: C, 40.59%; H, 4.43%; N, 8.90%.

However, kinetic runs using recrystallized 2-pyridone and using the sodium salt (assumed to be the dihydrate) gave identical second order rate constants.

1-Methyl-2-pyridone:

For use in kinetic experiments the commercial material (Aldrich) was converted to its hydrobromide salt: 1-methyl-2-pyridone was reacted with a slight excess of concentrated HBr in acetone. The solution was evaporated and the residue was recrystallized from acetone. After drying at 110°C, the crystals had a mp 174-177°C (lit.[142] 175-176°C). Proton NMR and IR spectra agreed with the literature.[142]

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*Problems of hydration were encountered by Spinner, who gave no melting point for this hydrated salt.[83,143]

2-Methoxypyridine:

The commercial material was used as received from Aldrich. Attempts to use its HBr salt (prepared as above for 1-methyl-2-pyridone) were unsuccessful since this salt undergoes hydrolysis (inferred from kinetic runs) to 2-pyridone upon standing in aqueous solution. Thus, a basic medium was employed for product studies (see later).

3-Bromo-1-methyl-2-pyridone:

To 3-bromo-2-pyridone (synthesis on pages 190 and 191) (0.45 g, 2.59 mmol) in 50 mL methanol was added an equivalent amount of sodium methoxide in 5 mL of methanol. After 5 min stirring, dimethyl sulfate (0.65 g, 5.2 mmol) was added and the solution warmed at 50-60°C for 3 hours. The resultant solution was made basic with NaOMe (pH 8-9, test paper), and 60 mL of 1:1 acetone/chloroform was added to complete precipitation of salts. The remaining solution was filtered and reduced to an oil which was dissolved in benzene, filtered again, and evaporated to give a slightly yellow oil (0.41 g, 85%), characterized by NMR and IR. The material used for kinetic runs was distilled, bp 117-120°C/0.1 mmHg (lit.[144] bp 120-125°C/0.5 mmHg).

5-Bromo-2-pyridone:

This was prepared as outlined in the literature.[83] For reasons of solubility the sodium salt was used for kinetic experiments. It was prepared as follows: in a minimum amount of water 5-bromo-2-pyridone was dissolved with an equivalent amount of NaOH. The solution was filtered, and acetone was added to the filtrate to precipitate the sodium salt which was filtered off and washed with acetonitrile. Recrystallization

from 2 parts EtOH/5 parts CH_3CN gave a product mp 349-50°C (dec). Proton NMR showed this to be the dihydrate, as did analysis.

Analysis: calculated for $C_4H_3BrNONa \cdot 2H_2O$: C, 25.89%; H, 3.02%; N, 6.04%; Br, 34.45%.

Found: C, 26.21%; H, 3.07%; N, 6.30%; Br, 34.29%.

5-Bromo-1-methyl-2-pyridone:

To an ethanolic solution of the sodium salt of 5-bromo-2-pyridone was added a slight excess of methyl iodide. The solution was refluxed for 10 min and evaporated to dryness. Recrystallization of the residue from benzene-ligroin gave slender white needles (60%), mp 65-67°C (lit.[144] 62-63°C), with appropriate spectra.

5-Bromo-2-methoxypyridine:

This compound was prepared by bromination of 2-methoxypyridine in acetic acid,[83] and as follows: to 2-methoxypyridine (1.1 g, 10 mmol) and KOH (0.28 g, 5 mmol)* in 60 mL water was added bromine (1.6 g, 10 mmol) in 60 mL 1 M aqueous KBr. The solution was made basic and extracted with 2 X 100 mL $CHCl_3$. The extract was dried over sodium sulfate and reduced to an oil (1.1 g, 63%). Proton NMR showed the title compound with a trace of the starting material.

The position of the bromine was confirmed by hydrolysis. The above oil was refluxed in 4 M sulfuric acid for 2.5 hours. The cooled solution was brought to pH 4 and evaporated to dryness. The solid was

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*Since 2-methoxypyridine (and probably 5-bromo-2-methoxypyridine) can be hydrolyzed in aqueous acid.

extracted with boiling benzene and evaporation of the solvent gave 5-bromo-2-pyridone, identical (NMR, IR, mp) to that prepared as above.

Bromination of 2-Pyridone

(a) In acetic acid. To 2-pyridone (1.9 g, 20 mmol) in 10 mL acetic acid was slowly added bromine (3.2 g, 20 mmol) in 40 mL acetic acid. When this solution was reduced 1/5 of its volume crystals of 3,5-dibromo-2-pyridone were deposited. Recrystallization gave this product (85%) with an IR spectrum as reported.[83]

(b) In aqueous base. The above amounts of 2-pyridone and bromine were added to an aqueous solution containing 1 equivalent of KOH. This resulting solution turned red and then black! After a few hours black needles were deposited which from their IR spectra were also the 3,5-dibromo product (85%).

(c) In water. During 5 min bromine (3.2 g, 20 mmol) in 40 mL 1 M aqueous KBr was added with stirring to 2-pyridone (1.9 g, 20 mmol) in 20 mL aqueous KBr. After 24 hrs. this solution deposited crystals which were filtered off and recrystallized from acetonitrile to give 2.72 g (78%) of 3-bromo-2-pyridone, identified by it's NMR and IR spectra.[83] Methylation of this material with dimethyl sulfate gave 1-methyl-3-bromo-2-pyridone as required.

(d) In D_2O (NMR study). A bromine solution in heavy water was added in 10 μL aliquots to a concentrated solution (~1 M) of 2-pyridone in D_2O. A number of NMR spectra were recorded. Because the signals were not well separated no estimate on the ratio of products was made.

Bromination of 1-Methyl-2-pyridone

(a) In acid solution. The title compound (0.73 g, 6.7 mmol) was dissolved in 10 mL of an aqueous solution which was 0.1 M in $HClO_4$ and 1 M KBr. To this solution was added with stirring bromine (1.07 g, 6.7 mmol) in 10 mL of the same medium. After standing for 3 hrs 0.6 g (67%) of the 3,5-dibromo product crystallized out. Its IR spectrum was identical to that reported.[83]

(b) In D_2O (NMR study). To a buffered $CH_3COOD/CH_3COONa/D_2O$ pD 4.0 was added bromine in 1 M KBr/D_2O solution in 10 μL aliquots. Various NMR spectra were run as a function of addition of bromine. The ratio of the reaction products was 7/2 of 3-bromo/5-bromo and some precipitate of the 3,5-dibromo compound.

4-Pyridone:

The technical grade material (Aldrich) was boiled in ethanol with charcoal and filtered. One equivalent of sodium ethoxide was added and the sodium salt of 4-pyridone was precipitated with acetone. Three recrystallizations from 10:1 acetonitrile/ethanol gave white needles mp 96-97°C.* Proton NMR in deuterium oxide and dimethylsulfoxide-d_6 suggested that there were two waters of crystallization. Elemental analysis was poor.

Analysis: calculated for $C_5H_4NONa \cdot 1.25H_2O$: C, 43.14%; H, 4.71%; N, 10.06%.

Found: C, 43.42%; H, 5.76%; N, 10.15%.

The nitrate salt was fortuituously prepared from an attempted

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* Spinner[83,143] gave no melting point for this compound.

nitration, as descibed by Albert and Barlin.[79] 4-Hydroxypyridinium nitrate was extracted from the salts with ethanol, treated with charcoal, and twice recrystallized from water mp 198-200°C (dec). Analysis: calculated for $C_5H_6N_2O_4$: C, 37.98%; H, 3.82%; N, 17.72%. Found: C, 37.94%; H, 3.95%; N, 17.58%.

The identical material can be obtained by acidifying a concentrated aqueous solution of 4-pyridone to pH 1 with HNO_3. After standing, the crystallized material is treated as above. The nitrate salt thus obtained, has identical IR and mp as the one prepared above.

1-Methyl-4-hydroxypyridinium bromide:

Practical grade 4-pyridone was partially dehydrated and purified by heating with two equivalents of hexamethyldisilazane in chloroform. The mixture was filtered by gravity and the solvent reduced to one half its original volume. Addition of ether gave white flakes mp 66-67°C (hydrate) (lit.[85] 148-9°C sublimed).

To this material (7.6 g, 68 mmol) and sodium methoxide (3.7 g, 68.5 mmol), dissolved in 10 mL methanol, was added with stirring dimethyl sulfate (8.83 g, 70 mmol) in 10 mL of methanol. The solution was heated for fifteen minutes and the pH was adjusted to 7-8 with addition of sodium bicarbonate. Repeated addition and evaporation with 1:1 acetone/chloroform, precipitated the salts. The oily residue was dissolved in acetone and slight excess of hydrobromic acid in 10 mL acetone, was added. After evaporation of solvent, the mass 6 g (46%) was recrystallized from methanol/ether mp 175-177,°C when dried at 110°C for one hour. The NMR spectrum was consistent with the structure.

Analysis: calculated for C_6H_8NOBr: C, 37.92%; H, 4.24%; N, 7.37%;

Br,42.05%.

Found: C, 37.80%; H, 4.16%; N, 7.22%; Br, 41.95%.

4-Methoxypyridine:

To 4-methoxypyridine-N-oxide (Aldrich), was slowly added two equivalents of phosphorous trichloride. There was a vigorous reaction at room temperature. The solution was stirred for 20 min and basified with aqueous ammonia to pH > 7. Afterwards, it was extracted with three 100 mL portions of chloroform, and dried over sodium sulfate. Removal of chloroform under reduced pressure yielded 85% of 4-methoxypyridine, whose odor was analogous to that of pyridine. Proton NMR agreed with the literature.[145]

Addition of bromine to 4-methoxypyridine in water, alcohol, or chloroform precipitated complexes. From water the complex has a mp 120-1°C and it is yellow. That obtained from chloroform is red mp 117-9°C. Its proton NMR is similar to 4-methoxypyridine. This product brominated acetone in chloroform and yielded the hydrobromide salt of 4-methoxypyridine, whose infrared is identical to that of 4-methoxypyridinium chloride.[145] Upon heating the bromine complex in water there is evolution of bromine gas with no detectable bromination product (cf. Den Hertog[90]).

3-Bromo-4-nitropyridine-N-oxide:[146,147]

The hydrochloride of 3-bromopyridine-N-oxide[136] (35 g) dissolved in 35 mL of c. H_2SO_4 was poured into a mixture containing 32 g KNO_3, 54 mL of concentrated HNO_3, 42 mL of concentrated H_2SO_4, and 28 mL of 20% oleum. This solution was heated slowly to 100°C and held there for

21 hours. The cooled solution was afterwards neutralized with sodium carbonate till nitric fumes abated. Ice was then added and more sodium carbonate was added until neutralization was hampered by insolubility of the carbonate. Ammonium hydroxide was then used to bring the solution to pH 7-8. The solution was cooled in an ice bath for 20 min, and the residual solid was suction-filtered and air-dried. The 3-bromo-4-nitropyridine-N-oxide, extracted four times with boiling chloroform, 25.1 g (69.9%) was recrystallized from benzene mp 150-2°C (lit.[136] 152-152.5°C, 57.5%).

4-Amino-3-bromopyridine:

This synthesis is a modification of Den Hertog's[148] procedure, for larger scale preparation. 3-Bromo-4-nitropyridine-N-oxide (5.0 g, 22.8 mmol) was dissolved in 100 mL of glacial acetic acid containing 8.33 g of iron powder. Gentle heat was applied to bring the temperature to 80-90°C with fast mechanical stirring. After 10 min the exothermic reaction brought the temperature to 110°C. The source of heat was removed and then reapplied after the temperature had fallen to maintain it at 80°C. Efficient stirring was maintained throughout the process. The reaction colour, after 40 min, had changed to light gray. The solution was heated for an additional 50 min, cooled, and basified beyond pH 8 with sodium carbonate and then ammonium hydroxide. Three 300 mL ether extractions and evaporations of solvent gave 3.42 g (86.7%) of product mp 66-68°C (lit.[148] 66-68°C) from light petroleum.

4-Amino-3-bromopyridinium Hydrosulphate:

An attempted diazotization of 4-amino-3-bromopyridine to 3-bromo-4-pyridone[149] was carried out with no cupric sulphate. Precipitation of the acidic salts with acetone and extraction with ethanol gave colourless crystals mp 216-218°C from ethanol. Its pK_a was determined spectrophotometrically at 25°C in 1 M aqueous KBr to be 7.15 ± 0.02. The HSO_4^- bands were visible in the IR spectrum (see Figure 37), while other bands were identical to a prepared sample of 4-amino-3-bromopyridinium hydrochloride.

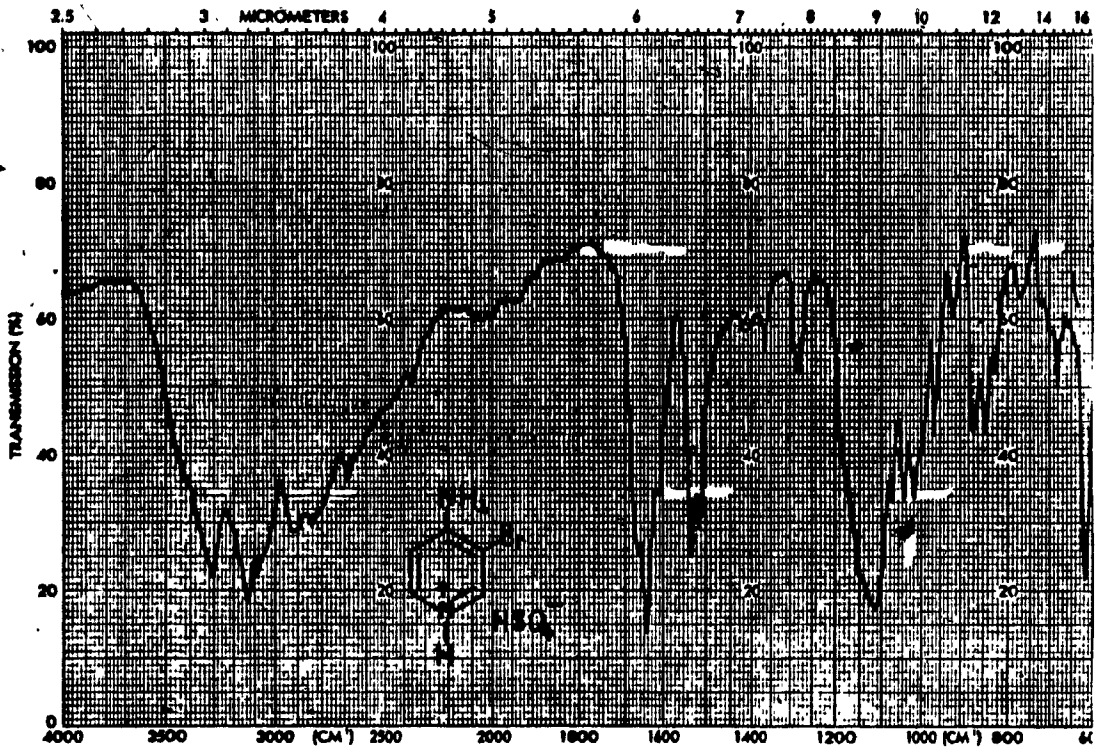

Figure 37. IR spectrum (KBr wafer) of 4-amino-3-bromopyridinium hydrosulphate.

Attempted Preparations of 3-Bromo-4-pyridone:

Yields for the halogenation reactions are based on the brominating agent.

Method (A): The literature procedure on 4-amino-3-bromopyridine[149] yielded < 5% total of the required 3-bromo-4-pyridone mp 227-229°C (lit.[149] 228-30°C) after several attempts.

Method (B): Using 2,4,4,6-tetrabromocyclohexa-2,5-dienone[150] in chloroform at 0°C and 4-pyridone, in equivalent amounts, gave, after extraction with light petroleum, a purple precipitate of the 3,5-dibromo-4-pyridone (> 65%). This product was identified by comparison of its IR spectrum with that of an authentic sample.

Method (C): An equimolar mixing of bromine and 4-pyridone in dioxane at room temperature slowly precipitated 3,5-dibromo-4-pyridone (60%).,

Method (D): The use of pyridinium hydrobromide perbromide and 4-pyridone in chloroform gave an even greater yield of the dibromo product: 72%.

Method (E): From 3-bromo-4-nitropyridine N-oxide, the corresponding 3-bromo-4-nitropyridine was prepared by the method of Ochiai[151], to give 2.7 g (73%) of an oily solid (lit.[152] by oxidation of the 4-amino analog mp 66-67°C). Treatment of this with $Ba(OH)_2 \cdot 8H_2O$ as outlined[153] gave an insoluble precipitate with an oily trace remaining after solvent evaporation.

But when 3-bromo-4-nitropyridine, prepared as above, was refluxed in 20% H_2SO_4 for two hours, cooled, neutralized, evaporated dry, extracted with ethanol, and again evaporated, gave a solid residue mp 103-107°C. This material was dissolved in a minimum amount of water, acetone (~45 mL) was added, filtered, and cooled to give some needles mp 200-5°C of similar infrared spectrum to the product of mp 103-7°C.

Some of the compound mp 103-7°C treated with bromine in ethanol, precipitated some 3,5-dibromo-4-pyridone. 3-Iodo-4-pyridone was synthesized[154] decomposing at 248-51°C (lit.[154] 289-292.5°C of mixture), and its IR spectrum was similar to the product mp 103-7°C. This was convincing evidence that impure 3-bromo-4-pyridone was prepared.

Method (F): Pyridine-N-oxide (Aldrich) was nitrated, as for 3-bromopyridine N-oxide, and hydrolyzed with hydrogen peroxide in base[155] to the 4-hydroxypyridine-N-oxide. Bromination of this product with $CCl_4/Br_2/H_2O/KBrO_3$[156] gave the same material yield (0.7 g) but of the 3,5-dibromo-4-hydroxypyridine-N-oxide 240-2°C dec (lit.[94] 241°C dec), and not of the 3-bromo product 263-4°C dec as reported. Proton NMR in D_2O/DSS showed one signal.

Other methods also failed (see bromination of 4-pyridone).

One-step Preparation of 3-Bromo-4-pyridone:

Technical grade 4-pyridone (0.951 g, 10 mmol) was dissolved in 50 mL of distilled water containing 1.0 g of anhydrous sodium acetate. The pH of the solution was adjusted with acetic acid to 4.2-4.4 and cooled in an ice bath. A bromine solution was prepared (1.6 g, 10 mmol) in 50 mL of 1 M aqueous KBr. This solution was added to the former at 0°C with efficient stirring over a 45-minute period. A precipitate of 3,5-dibromo-4-pyridone 0.33 g, 26.2% based on added bromine, was filtered off. The mother liquors were evaporated dry on a water bath and the residual solid extracted with ethanol. The ethanol extract contained 4:1 3-bromo-4-pyridone/4-pyridone as inferred from the integration of the proton NMR signals. Separation of the inorganic

salts from this residue was effected by boiling with one liter of acetone and filtering the hot solution. The residue (1.55 g) of such extraction contained 80% excess 3-bromo-4-pyridone (73.8% based on added bromine). Treatment with charcoal, in boiling water and recrystallization from water gave the title compound 0.48 g mp 229-31°C (lit.[149] 228-30°C).

No optimization of reaction was attempted but doubling the concentration of reactants caused a 1.6 fold increase in the percent formation of the dibromo product.

1-Methyl-3-bromo-4-hydroxypyridinium Bromide:

To 3-bromo-4-pyridone (1.5 g, 8.6 mmol) was added 0.48 g of potassium hydroxide in 30 mL of methanol. This solution was refluxed for two hours with 1.6 mL (18 mmol) of dimethyl sulfate. The cooled solution was basified with sodium methoxide. Addition of 200 mL of acetone and 10 mL of ether precipitated the salts. Further removal of salts was accomplished by repeated treatment with 10:1 chloroform/acetone and solvent evaporation. The residual oil was dissolved in chloroform, gravity-filtered, and the solvent was evaporated. To the oil, dissolved in acetone, was added a slight excess of hydrobromic acid to precipitate the title compound 1.57 g (67.7%). Recrystallization from acetonitrile (1 g/300 mL) gave transparent needles mp 253-5°C (dec). The IR of this material is reported below: Figure 38. The NMR (D_2O/DSS) is reported in Table XXIII (page 114).

Analysis: calculated for $C_6H_7NOBr_2$: C, 26.80%; H, 2.62%; N, 5.21%; Br, 59.42%.

Found: C, 27.08%; H, 2.69%; N, 5.23%; Br, 59.48%.

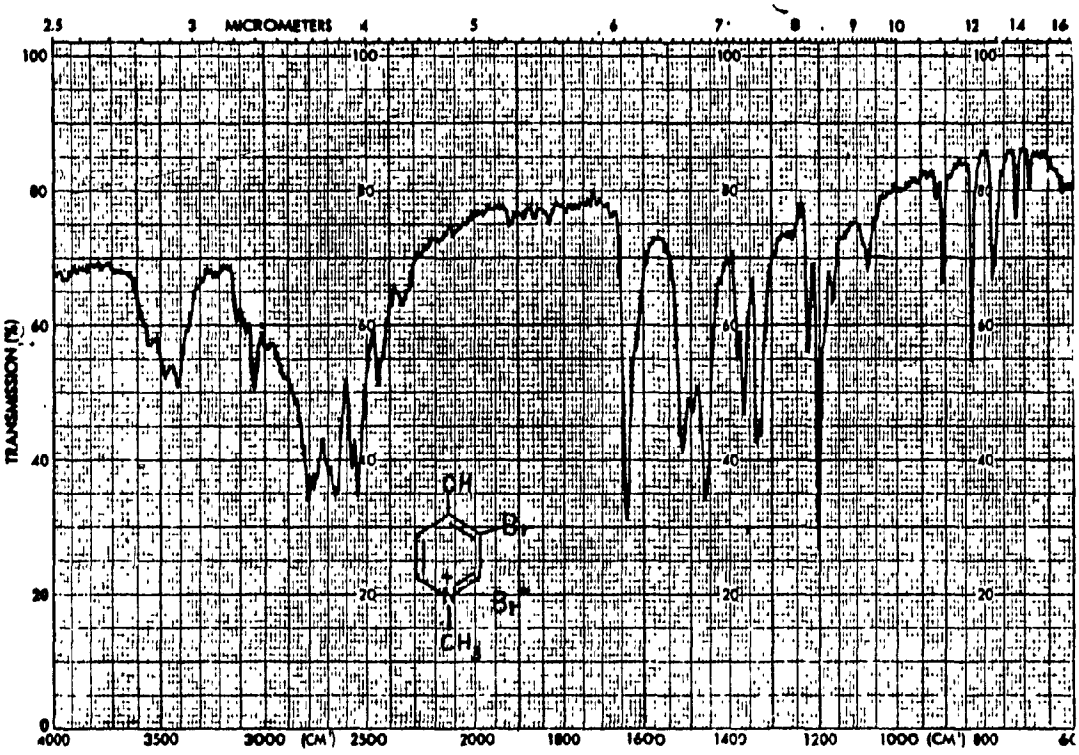

Figure 38. IR spectrum (KBr wafer) of 3-bromo-4-hydroxy-1-methylpyridinium bromide.

Reaction of 4-Pyridone with Bromine:

(a) In acid: To 4-pyridone hydrate, purified as for the preparation of 1-methyl-4-hydroxypyridinium bromide, (1.13 g, 10 mmol) dissolved in 25 mL of 48% HBr was added bromine (1.60 g, 10 mmol), dissolved in 25 mL of the same medium. The addition lasted 30 minutes. Ice was added and the pH adjusted to 3 with sodium carbonate. The volume of the solution was reduced on a water bath and upon cooling 0.923 g (3.65 mmol) 73%, based on added bromine, of 3,5-dibromo-4-pyridone precipitated. Its IR spectrum was identical to that reported.[74] Proton NMR of the residual solid indicated the presence of 2:5 3-bromo-4-pyridone/4-pyridone.

(b) In aqueous solution of 1 M KBr: Same procedure as above yielded

(0.842 g, 67% based on added bromine) of the dibromo product.

(c) In one equivalent of KOH: Same procedure applied to an aqueous 1 M KBr solution yielded 1.08 g of precipitated 3,5-dibromo-4-pyridone (86.0%, based on added bromine).

In all cases then the 3-bromo-4-pyridone was the minor product of the reaction, except for the reaction in acetate buffer.

Apparatus

An Aminco-Morrow Stopped Flow accessory, using an Aminco DW-2 UV-Visible Spectrophotometer operating in the dual wavelength mode, was used for kinetic UV measurements. Optical density decreases were input through a Biomation 805 Waveform recorder and monitored on an oscilloscope. Traces with better signal-to-noise ratio and less distortion, were plotted from the Biomation onto the Aminco X-Y recorder through an adjustable dropping resistor. Conventional UV measurements were performed with the spectrophotometer operating in the split-beam mode.

Kinetic runs for the pyrimidones were at $30.0 \pm 0.1^{\circ}C$. Temperature control was maintained by a Lauda (model No. RC-20B) constant-temperature circulating bath. This specific temperature was chosen for comparison of earlier kinetic work.[18b,c,19] For all other substrates the temperature was maintained at $25.0 \pm 0.1^{\circ}C$.

Proton NMR spectra were taken on a Varian A-60 and T-60 NMR instruments. Infrared spectra were recorded from a Perkin-Elmer 599B

Infrared Spectrophotometer.

For gas chromatographic work a 3 ft stainless steel column packed with Chromosorb-W HP coated with 3% Carbowax 20 M was attached to a conductivity detector. The column was generously supplied by Dr. R. T. Rye. The temperature of the column was kept at 145°C and that of the detector at 100°C. The injection port temperature was kept at 90°C (mid-range). The flow rate of the helium gas was also kept at mid-range.

Methods

Bromine solutions were prepared by weight in 1 M aqueous KBr for all pH regions: usually 0.5000 M or 1.000 M, and diluted appropriately. For the pyrimidones and derivatives, also for some of the preliminary studies on the pyridones, the buffer solutions in 0.1 M aqueous KBr were prepared following Perrin[157] and always checked using a Corning digital 110 pH meter. For kinetic studies in 1 M aqueous KBr the universal buffer[158] system: $H_3PO_4/CH_3COOH/H_2BO_3/NaOH$ was used for convenience. The ionic strength of this buffer system was as Perrin's: I = 0.01 M. All inorganic reagents were of analytical grade. Sodium hydroxide solutions were prepared from commercial Anachemia standard volumetric concentrates.

For the kinetic studies one drive syringe contained the substrate

in the chosen medium, and the other contained bromine (usually 1×10^{-4} M) in the same medium. All concentrations given in the text are after mixing. Reactions were followed by monitoring the change at 266 nm (λ_{max} of Br_3^-) log $\epsilon = 4.54$[63] relative to that at 240 or 340 nm where there is little or no change. Sometimes the monitoring wavelength was adjusted (usually to longer wavelengths) since products or substrate absorbance was too large to permit a baseline balance. The slit was in most instances 7.0 nm. This allowed for less noise in the traces.

The pseudobase kinetic studies were conducted in the manner of Bunting and Meathrel.[62] One drive syringe contained 5×10^{-4} M solution of the N,N-dimethyl-4-oxo-pyrimidinium cation 10d (or its pseudobase 14d) in 0.1 M aqueous KBr, while the other contained a buffer of pH > pK_{R+} also in the same medium and of twice the concentration given in Perrin.[157] Thus, after mixing, the solution conditions were the same as those in the bromination studies. The disappearance of 10d (or 14d) was monitored at 289 nm relative to 320 nm (spectral minimum). Good first order behaviour was observed for > 90% reaction. Analysis of ln $(D - D_\infty)$, where D and D_∞ are optical densities at time t and infinity respectively, versus time gave pseudo-first-order rate constants k_1^{obsd} with a correlation coefficient > 0.9995. The reproducibility of k_1^{obsd} depended upon the speed of the reaction. For the faster runs near the limit of the apparatus it was about 10% but for the slower runs it was less than 5%.

For product analysis of phenol bromination gas chromatograpy was used. The conditions for bromination were kept as close as possible to

those for the kinetics. Bromine 0.0125 M in 200 mL of 1 M KBr (the concentration of bromine was kept constant while that of phenol was varied) and phenol 0.125 M in 200 mL of the same solution, were mixed, in one motion, into a fast-stirring solution (300 mL of 1 M KBr) and allowed to react for one hour. The solution was then acidified with concentrated hydrochloric acid filtered if excessive precipitate was present, and extracted with two 200 mL portions of chloroform. After reducing the solvent to about 10 mL, 5 mL of 1,1,1,3,3,3-hexamethyldisilazane was added, filtered, and the filter paper washed carefully with chloroform. The solution was again evaporated down to 5 mL and placed in a 10.0 mL volumetric flask. It was then diluted to the mark with the silylating agent and allowed to stand for 24 hours.

The pure compounds and known mixtures were prepared using chloroform and excessive silylating agent only, for qualitative and quantitative study. 2,6-Dibromophenol gives needles after about an hour which slowly dissolve into the same medium when shaken. All the polybrominated phenols do not elute from the column used. Attempts to do the same experiment with 2-pyridone and its N-methyl derivative failed for the same reason.

Injection volumes were, in general, 5 μL but 1 μL injections were used for calibration graph. Retention times were in ascending order phenol < 2-bromophenol < 4-bromophenol. From the GC chromatographs it was evident that even for a 1:1 reaction in acid, polybromination takes place: phenol is still present in the mixture.

Kinetic Observations and Treatment of Data

The substrates studied and their corresponding bromo products give rise to strong absorption bands in the middle of the UV region (240–290 nm). A rapid decrease in absorption of the tribromide ion (λ_{max} 266 nm) is noted upon mixing aqueous Br_2/KBr and substrate solutions.

For the cases where the initial substrate is greater than or equal to the initial bromine concentration, application of the Beer-Lambert law[87] and the appropriate integrated rate equations has been shown[49c] to lead to the well-known expressions for first order (equation V.1 and second order (equations V.2 and V.3):

$$\ln \frac{D_o - D_\infty}{D - D_\infty} = k_1 t \qquad \text{V.1}$$

$$\ln \frac{([P_i]_o - X)}{([Br_2]_o - X)} = \ln\left\{\frac{[P_i]_o}{[Br_2]_o}\right\} + ([P_i]_o - [Br_2]_o)\, k_2 t \qquad \text{V.2}$$

where the amount of bromine that has reacted at time t is:

$$X = \frac{(D_o - D)\ [Br_2]_o}{(D_o - D_\infty)}$$

D_o, D, and D_∞ are the optical densities of the solution initially, at any time t, and at infinite time respectively. The initial substrate and bromine concentrations are denoted $[P_i]_o$ and $[Br_2]_o$ respectively.

For the second-order case where $[P_i]_o = [Br_2]_o$:

$$\frac{(D_o - D)}{(D - D_\infty)} = [BF_2]_o \, k_2 \, t \qquad V.3$$

In the Normal Treatment of data a least-squares regression is carried out for equation V.1 to calculate k_1 as the slope.

If a set of data points separated by a constant time interval (Δt) is considered such that D_1, D_2, ..., D_n are the optical densities at t_1, t_2, ..., t_n and D_1', D_2', ..., D_n' are those at $t_1 + \Delta t$, $t_2 + \Delta t$, ..., $t_n + \Delta t$, then other treatments may be carried out for equation V.1 which are useful where D_∞ is not accurately known.

The Swinbourne Treatment[49c,58] may be employed to determine D_∞. Substitution of two different points into the exponential form of equation V.1, dividing the resulting equations, and rearranging:

$$D = D_\infty (1 - \exp(k_1 \Delta t)) + D' \exp(k_1 \Delta t) \qquad V.4$$

Therefore, least-squares analysis of D versus D' allows k_1 to be obtained fron the slope $\{\exp(k_1 \Delta t)\}$ and D_∞ from the slope and intercept since:

$$D_\infty = \frac{\text{Intercept}}{(1 - \text{Slope})} \qquad V.5$$

For best results the data should span a period of time greater than one half-life and preferably greater than two. The value of (Δt) should be between one half and one half-life.

The value of D_∞ obtained in this manner can be inserted into the Normal method of analysis. The values of k_1^{obsd} referred in this

thesis were all determinedby the Normal treatment utilizing Swinbourne value of D_∞ since this gave better correlated values.

The Guggenheim Treatment[25,59,49c] of data may be employed when D_∞ is not known. If, as in the Swinbourne method above, the two exponential forms of equation V.1 containing D and D' are subtracted then:

$$(D' - D) = (D_o - D_\infty)\exp(-k_1 t)\{\exp(-k_1 \Delta t) - 1\} \qquad V.6$$

and therefore:

$$\ln(D' - D) = \ln\{(D_o - D_\infty)(\exp(-k_1 \Delta t) - 1)\} - k_1 t \qquad V.7$$

Linear regression analysis of $\ln(D' - D)$ against t should yield a straight line of slope $-k_1$. For optimum results the data should cover at least two half-lives and (Δt) should be between one half and one half-life.

The cases where $(n-i)[P_i]_o = [Br_2]_o$ (n-i is the number of sites of attack on the substrate P_i below) may need some clarification with respect to absorbances variations of tribromide ion, substrates, and products. The generalized process which accounts for consecutive brominations is shown below:

$$P_0 \xrightarrow{Br_2} P_1 \xrightarrow{Br_2} P_2 \xrightarrow{Br_2} \ldots P_i \xrightarrow{Br_2} \ldots P_n$$

where $P_i = \sum_j P_{ij}$ and also $C_i P_i = D_i$. P_i are the starting subtrates or intermediate products, P_n are the final products, C_i is a global

extinction coefficient for the sum of the species at each step in the bromination, and D_i is the optical density of species i. As can be seen from computer simulations (see Figure 29) only the species giving rise to the rate-determining step and the final products need to be considered. These conditions lead to the following equations of mass-balance where the i^{th} step is rate-limiting:

$$[P_i]_o = [P_i] + [P_n] \qquad V.8$$

$$[Br_2]_o = [Br_2] + (n - i)[P_n] \qquad V.9$$

From the initial condition above:

$$[Br_2]_o = (n - i)[P_i]_o \qquad V.10$$

Combining the last three equations:

$$[Br_2] = (n - i)\,[P_i] \qquad V.11$$

The equations from the Beer-Lambert's law[87] are:

$$D_o = C_i\,[P_i]_o + C_{Br}\,[Br_2]_o \qquad V.12$$

$$D_\infty = C_n/(n - i)\,[Br_2]_o \qquad V.13$$

$$D = D_i + D_n + C_{Br}[Br_2] \qquad V.14$$

By substitution of equations V.12 and V.13:

$$D_i = \{C_i/(n - i) - C_n/(n - i) + C_{Br}\}\,[Br_2] + C_n/(n - i)\,[Br_2]_o \qquad V.15$$

The appropriate quantities needed for the second-order equation $\{[Br_2]_o/[Br_2] - 1 = [Br_2]_o k_2 t\}$ are:

$$D_o - D = \{C_i/(n - i) - C_n/(n - i) + C_{Br}\} [Br_2]_o' - \{C_i/(n - i) - C_n/(n - i) + C_{Br}) [Br_2] \quad V.16$$

$$D - D_\infty = \{C_i/(n - i) - C_n/(n - i) + C_{Br}\} [Br_2] \quad V.17$$

Therefore the final expression is the usual:

$$\frac{D_o - D}{D - D_\infty} = \frac{[Br_2]_o}{[Br_2]} - 1 = [Br_2]_o \, k_2 \, t \quad V.18$$

The purpose of this exercise was to show that regardless of the number of intermediate products in the reaction the contribution to the total absorbance (i.e. the terms for the extinction coefficients) cancel in the final expression making it identical to the one derived assuming one reaction product (equation V.3).

Computer Programs

All calculations were performed on a CDC Cyber 172 Digital Computer using routines of least-squares fit to the data and the above integrated equations. The routines, written by Dr. O.S. Tee, were coded in BASIC.

The NEW1ST program treats the data in three different ways: Guggenheim,[25,59] Swinbourne,[58] and Normal. The Normal analysis using Swinbourne D_∞ gave the better correlated values (c-c > 0.9995) and was the accepted treatment. With the observed value of D_∞, the Normal treatment gave poorer correlated values but the rate constants from the

three methods usually agreed to within 5%.

NEWSEC- There are two versions of this program. For the case where reactants were employed in stoichiometric amounts $\{(n-i)[P_i]_o = [Br_2]_o\}$ it solves for the identical equations V.3 or V.18, giving poorer correlation coefficients (but usually > 0.9993) since D_∞ is a critical quantity and must be adjusted.

The second version of the program applies when one reactant is in larger amounts over the other. Equation V.2 is used which is closer to that for a first-order analysis and not as dependent on D_∞. This value is approached much more rapidly and thus was more readily determinable. Better correlated data were obtained (c-c > 0.9995) for 90% reaction.

ZERO- This is the regression for a straight line:

$$[Br_2]_o - [Br_2] = k_o\, t \qquad \text{V.19}$$

and by substitution of equations V.12-V.14:

$$\frac{D - D_\infty}{D_o - D_\infty} = 1 - \frac{k_o}{[Br_2]_o}\, t \qquad \text{V.20}$$

This program regresses the left hand side of equation V.20 versus t. All kinetic runs analyzed in this fashion gave correlation coefficient > 0.9995 for 90% reaction.

ALLMIX- This program analyzes equation I.28:

$$\frac{k_{-1}[H^+]}{k_2} \ln\left\{\frac{[Br_2]_o}{[Br_2]}\right\} + ([Br_2]_o - [Br_2]) = \frac{k_1[H^+][P]_o\, t}{([H^+] + K)} \qquad \text{I.28}$$

This equation contains a first-order term and a zero-order term whose relative importance depends upon $[H^+]$ and $[Br_2]$. The approaches[19] to its solution in this program are three. First treat k_1 as known (available from separate experiments), subtract the zero-order component, find the ratio k_{-1}/k_2 by least-squares fitting, and calculate a first-order constant $\{k_1^{obsd} = (k_1k_2[P]_o)/(k_{-1}([H^+] + K))\}$. Second, assume a value of k_{-1}/k_2 (may be estimated from results at lower pHs), subtract the first-order term, and find a zero-order rate constant $\{k_o^{obsd} = (k_1[H^+][P]_o)/([H^+] + K)\}$ by fitting. The third approach[17a] is to multiply through by $\{[Br_2]_o/([Br_2]_o - [Br_2])\}$ a regression of $\{[Br_2]_o/([Br_2]_o - [Br_2])\ \ln([Br_2]_o/[Br_2])\}$ versus $\{([Br_2]_o\ t)/([Br_2]_o - [Br_2])\}$ gives $\{(k_1k_2[P]_o)/(k_{-1}([H^+] + K))\}$ as the slope and $\{(k_2[Br_2]_o)/(k_{-1}[H^+])\}$ as the intercept. These estimates may be adjusted to give the best correlation coefficients (> 0.999 sometimes > 0.9995). All data spanned at least 85% reaction.

The program UVPROS was written by the author to handle the analysis of products from the UV spectra of mixtures. It requires coefficients of the mass-balance equations with initial concentrations, the actual wavelengths, the extinction coefficients for each individual species at the different wavelengths, and the absorbance values of the mixture at the different wavelengths. The data is handled by (1) multiple regression without use of mass-balance equations, (2) multiple regression employing the mass-balance equations, and (3) using two mass-balance equations and (n - 2) absorbance values of the mixture and

solving for the n species in solution. If N is the total number of wavelengths for the mixture input into the program, then there will be $\{N!/[(n - 2)!(N - n + 2)!]\}$ different solutions. Each solution is assessed: if even one value of concentration is negative or greater than or less than 20% from the corresponding value in analysis (2) then the wavelengths employed are flagged and may be omitted from subsequent analysis. The entire process (from analysis (1)) may be repeated with a different number N so as to give positive concentration values with least standard deviation.

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VII. APPENDIX

The aim of this appendix was to illustrate that for nonlinear differential equations, derived in this work from kinetic rate laws, there exists a fundamental solution if particular stoichiometric ratios of reactants are maintained during their initial mixing. This solution demonstrates that the overall rate is determined by the slowest process of the reaction. In recent years, however, the emphasis has shifted from more "classical" mathematical goal of finding exact (i.e., analytical) solutions to integral equations and differential equations to the more realistic attempts at the qualitative characterization of solutions. This change in approach follows necessarily from an increasing preoccupation with nonlinear problems for which exact analytical solution are unlikely.[134] In agreement with Somorjai, there is no single best "recipe" for solution (even if a unique solution does exist), and inspired guessing combined with perseverance plays an important role.[134] Without recourse to a steady state treatment, the complete non-linear differential equations derived below have been obtained by a process similar to that described by Benson.[135] The solution(s) evolve from the boundary conditions where the reactants are in stoichiometric[100,101] amounts. However, the graphical method of Schwemer and Frost[100] involves interpolation to obtain the various rate

constants and similarity with the method below disappears. Bromination of phenol is a multistep process analogous to the alkaline hydrolysis of triethyl citrate. In this hydrolysis, Svirbely et al.[101] use an iterative method and a steady state assumption to obtain the seven rate constants. From perusal of the literature, it can be said that exact solutions of competitive-consecutive second-order reactions are hitherto unknown!

Exact Solutions of Consecutive Second-Order Reactions

The operators given below have the following significance: $([\ ]') = (d[\ ]/dt)$, $([\ ]'') = (d^2[\ ]/dt^2)$, $([\ ]''') = (d^3[\ ]/dt^3)$. All differentiations, whether directly expressed or not, are with respect to time.

1. Linear. For the process:

$$A \underset{}{\overset{K_{a1}}{\rightleftharpoons}} A^- + H^+$$

$$A + Br_2 \xrightarrow{k_2} B$$

$$A^- + Br_2 \xrightarrow{k_1} B$$

$$B \underset{}{\overset{K_{a2}}{\rightleftharpoons}} B^- + H^+$$

$$B^- + Br_2 \xrightarrow{k_3} C$$

$$B + Br_2 \xrightarrow{k_4} C$$

Let $k_5 = k_2 + k_1K_{a1}/[H^+]$ $\quad k_6 = k_4 + k_3K_{a2}/[H^+]$

$a = 1/(1 + K_{a2}/[H^+])$ $\quad b = 2([H^+] + K_{a1})/([H^+] + K_{a2})$

$$([A]') = -k_5[A][Br_2] \quad \text{.....} \quad 1.1$$

$$-([Br_2]') = k_5[A][Br_2] + k_6[B][Br_2] \quad \text{.....} \quad 1.2$$

From the mass balance:

$$[B] = a(2[A]_o - [Br_2]_o) - 2b[A] + a[Br_2] \quad \text{.....} \quad 1.3$$

where $[A]_o$ and $[Br_2]_o$ are the initial stoichiometric concentration of substrate and bromine respectively. Substitution of equation 1.3 into equation 1.2 leads to:

$$-([Br_2]')/Br_2 - ak_6(2[A]_o - [Br_2]_o) - ak_6[Br_2] = (k_5 + bk_6)[A] \ldots \quad 1.4$$

Differentiating 1.4 with respect to time and substituting equation 1.1 for $([A]')$:

$$-([Br_2]'')/Br_2 + ([Br_2]')^2/[Br_2]^2 - ak_6([Br_2]') =$$
$$-k_5(k_5 - bk_6)[A][Br_2] \quad \text{.....} \quad 1.5$$

Dividing equation 1.4 by 1.5 to eliminate [A] and rearranging:

$$(k_5 + ak_6)([Br_2]')[Br_2]^2 + ak_5k_6(2[A]_o - [Br_2]_o)[Br_2]^3 +$$
$$ak_5k_6[Br_2]^4 + ([Br_2]'')[Br_2] - ([Br_2]')^2 = 0 \quad \text{.....} \quad 1.6$$

If $[Br_2]_o = 2[A]_o$ then the exact solution of this nonlinear differential equation is:

$$[Br_2] = 1/\{(k^{obsd})t + (1/[Br_2]_o)\} \quad \text{.....} \quad 1.7$$

By differentiation of 1.7 and substitution of the various differentials into 1.6, it is a trivial exercise to show that this is indeed the solution of equation 1.6 for all the time domain. Moreover, after this substitution, it is possible to solve for k^{obsd}:

$$-(k_5 + ak_6)(k^{obsd}) + ak_5k_6 + (k^{obsd})^2 = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 1.8$$

This factors into:

$$(k^{obsd} - k_5)(k^{obsd} - ak_6) = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 1.9$$

Replacing the expressions for a, k_5, and k_6 the two roots are:

$$(k^{obsd}) = (k_2 + k_1K_{a1}/[H^+]) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 1.10$$

$$(k^{obsd}) = (k_4[H^+] + k_3K_{a2})/([H^+] + K_{a2}) \quad \ldots\ldots\ldots\ldots\ldots \quad 1.11$$

The smaller of the last two functions, for varying pH, appears to determine the overall rate constant for the reaction. This can be seen from the separate rate profiles determined under pseudo-first-order conditions for A and B, equations 1.10 and 1.11, respectively, and then contrasting the second-order rate constant for the case $2[A]_o = [Br_2]_o$.

2. Parallel. For the process:

$$A + Br_2 \xrightarrow{k_1} B$$

$$A + Br_2 \xrightarrow{k_2} C$$

$$B + Br_2 \xrightarrow{k_3} D$$

$$C + Br_2 \xrightarrow{k_4} D$$

The various equilibria have been eliminated from the process for clarity. All operators have been defined for the linear process above. The equations describing this system are:

$$2[A]_o - [Br_2]_o = 2[A] + [B] + [C] - [Br_2] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 2.1$$

$$([A]') = -(k_1 + k_2)[A][Br_2] \quad \text{.....} \quad 2.2$$

$$([B]') = k_1[A][Br_2] - k_3[B][Br_2] \quad \text{.....} \quad 2.3$$

$$-([Br_2]') = (k_1 + k_2)[A][Br_2] + k_3[B][Br_2] + k_4[C][Br_2] \quad \text{.....} \quad 2.4$$

Combining equations 2.1 and 2.4 to eliminate [C]:

$$-([Br_2]') = (k_1 + k_2)[A][Br_2] + k_3[B][Br_2] + k_4(2[A]_o - [Br_2]_o - 2[A] - [B] + [Br_2])[Br_2] \quad \text{.....} \quad 2.5$$

This can be rewritten as:

$$-([Br_2]')/[Br_2] - k_4[Br_2] = a[A] + b[B] + c \quad \text{.....} \quad 2.5a$$

where $a = k_1 + k_2 - 2k_4$

$b = k_3 - k_4$

$c = k_4(2[A]_o - [Br_2]_o)$

Differentiating equation 2.5a:

$$-([Br_2]'')/[Br_2] + ([Br_2]')^2/[Br_2]^2 - k_4([Br_2]') = a([A]') + b([B]') \quad \text{.....} \quad 2.6$$

Substituting for [A'] and [B'] from equations 2.2 and 2.3 the right hand side of equation 2.6 becomes:

$$= -a(k_1 + k_2 - bk_1)[A][Br_2] - bk_3[B][Br_2] \quad \text{.....} \quad 2.6a$$

Dividing by $[Br_2]$:

$$-([Br_2]'')/[Br_2]^2 + ([Br_2]')^2/[Br_2]^3 - k_4([Br_2]')/[Br_2] = d[A] - e[B] \quad \text{.....} \quad 2.7$$

where $d = -a(k_1 + k_2) + bk_1$

$e = bk_3$

Combining equations 2.5a and 2.7 to eliminate [B]:

$$-([Br_2]'')/[Br_2]^2 + ([Br_2]')^2/[Br_2]^3 - (k_3 + k_4)([Br_2]')/[Br_2] - k_4k_3[Br_2] = (ak_3 + d)[A] + ck_3 \quad \ldots\ldots \quad 2.8$$

Differentiating equation 2.8 with respect to time, and substituting for ([A]') (equation 2.2):

$$-([Br_2]''')/[Br_2]^2 + 4([Br_2]'')([Br_2]')/[Br_2]^3 - 3([Br_2]')^3/[Br_2]^4 - (k_4 + k_3)([Br_2]')^2/[Br_2]^2 - k_4k_3([Br_2]') = -(k_1 + k_2)(ak_3 + d)[A][Br_2] \quad \ldots\ldots\ldots\ldots \quad 2.9$$

Combining equations 2.8 and 2.9 to eliminate [A] and rearranging:

$$-([Br_2]''')/[Br_2]^2 + 4([Br_2]'')([Br_2]')/[Br_2]^3 - 3([Br_2]')^3/[Br_2]^4 - (k_1 + k_2 + k_3 + k_4)\{([Br_2]'')/[Br_2] + ([Br_2]')^2/[Br_2]^2\} - \{(k_1 + k_2)(k_3 + k_4) + k_4k_3\}([Br_2]') - k_4k_3(k_1 + k_2)[Br_2]^2 - k_3k_4(k_1 + k_2)(2[A]_o - [Br_2]_o)[Br_2] = 0 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 2.10$$

If $[Br_2]_o = 2[A]_o$ then the general function for the solution of this differential equation is:

$$[Br_2] = 1/\{(k^{obsd})t + 1/([Br_2]_o)\} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 2.11$$

Differentiating 2.11 and substituting into equation 2.10 the expression for k^{obsd} is:

$$(k^{obsd})^3 - (k_1 + k_2 + k_3 + k_4)(k^{obsd})^2 + [(k_3 + k_4)(k_1 + k_2) + k_3k_4](k^{obsd}) - k_3k_4(k_1 + k_2) = 0 \quad \ldots\ldots\ldots \quad 2.12$$

which factors into:

$$(k^{obsd} - k_3)(k^{obsd} - k_4)(k^{obsd} - [k_1 + k_2]) = 0 \quad \ldots\ldots\ldots\ldots \quad 2.13$$

The three roots are:

$$k^{obsd} = [k_1 + k_2] \quad \ldots\ldots\ldots\ldots \quad 2.14$$

$$k^{obsd} = k_3 \quad \ldots\ldots\ldots\ldots \quad 2.15$$

$$k^{obsd} = k_4 \quad \ldots\ldots\ldots\ldots \quad 2.16$$

Depending upon the acidity of the buffered solution, k^{obsd} will equal the slowest process of the reaction at a given pH.

For a combination of linear and parallel consecutive second order reactions, as in the case of phenol, it is possible to find the non-linear differential equation in the same manner. Such a derivation was avoided here because it is too lengthy. From computer simulations*,[121] it can be seen that the general solution $[Br_2] = 1/\{(k^{obsd})t + (1/[Br_2]_o)\}$ applies for all pH's where $3[A]_o = [Br_2]_o$.

The situation to be expected when the kinetics of bromination are done under pseudo-first-order conditions will now be considered. For a truly competitive consecutive second-order process, the observed second-order rate constant derived from pseudo-first-order analysis may be as much as m times greater than that obtained under consecutive second-order conditions, where m is the number of equivalents of bromine consumed as a result of the rate-limiting step. This assertion evolved from the following analysis.

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* Dr. R. T. Rye guided us to in the use and logic of this computer program.

3. Cases 1-3. Consider case 1 where a substrate A (this may be phenol) is polybrominated (all reactions are irreversible).

$$A + Br_2 \xrightarrow{k_1} B$$

$$A + Br_2 \xrightarrow{k_2} C$$

$$B + Br_2 \xrightarrow{k_3} D$$

$$C + Br_2 \xrightarrow{k_4} D$$

$$C + Br_2 \xrightarrow{k_5} E$$

$$E + Br_2 \xrightarrow{k_6} F$$

$$D + Br_2 \xrightarrow{k_7} F$$

In the analysis of the data obtained under pseudo-first-order conditions ($[A]_o >> [Br_2]_o$) it was assumed that mainly one product is formed. However, this is not true, for instance, in the case of the phenoxide reaction.[115]

Assume ($k_1 + k_2$) is the slowest process in the pseudo-first-order case, the actual overall rate is:

$$-([Br_2]') = (k_1 + k_2)[A][Br_2] + k_3[B][Br_2] + (k_4 + k_5)[C][Br_2] + k_6[E][Br_2] + k_7[D][Br_2] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad 3.1$$

Assume that all the intermediates (B, C, D, E) formed approximate a steady state. This, in fact, is always true in a pseudo-first-order case since $[A]_o = [A]_t$ for all the time domain. Then:

$$([B]') = 0 = k_1[A][Br_2] - k_3[B][Br_2] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 3.2$$

$$[B] = (k_1/k_3)[A]$$

$$([C]') = 0 = k_2[A][Br_2] - (k_4 + k_5)[C][Br_2] \quad \text{.....} \quad 3.3$$

$$[C] = (k_2/(k_4 + k_5))[A]$$

$$([D]') = 0 = k_3[B][Br_2] - k_7[D][Br_2] + k_4[C][Br_2] \quad \text{.....} \quad 3.4$$

$$[D] = [(k_1/k_7) + k_2k_4/(k_4 + k_5)k_7][A]$$

$$([E]') = 0 = k_5[C][Br_2] - k_6[E][Br_2] \quad \text{.....} \quad 3.5$$

$$[E] = (k_2k_5/(k_4 + k_5)k_6)[A]$$

Substitution of [B], [C], [D], and [E] into the rate expression equation 3.1 obtains:

$$-([Br_2]') = 3(k_1 + k_2)[A][Br_2] \quad \text{.....} \quad 3.6$$

Thus, k_2^{obsd} in pseudo-first-order case is three times greater than the quaesitum* of $(k_1 + k_2)$ which is equal to k_2^{obsd} from consecutive second-order analysis.

Consider the linear case 2, where B may be 4-bromophenol, and the disappearance of B is the rate-determining step ($[B]_o >> [Br_2]_o$).

$$B + Br_2 \xrightarrow{k_3} D$$

$$D + Br_2 \xrightarrow{k_7} F$$

The overall rate law is:

$$-([Br_2]') = k_3[B][Br_2] + k_7[D][Br_2] \quad \text{.....} \quad 3.7$$

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* The word "quaesitum" is defined in the Webster dictionary as: the actual value of a quantity.

A steady state assumption on D (i.e. for $[D] = \{k_3/k_7\}[B]$) gives a rate law:

$$-([Br_2]') = 2(k_3)[B][Br_2] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 3.8$$

Thus, k_2^{obsd} for pseudo-first-order analysis, is twice greater than the actual value k_3.

Consider the <u>parallel</u> case 3, where C may be 2-bromophenol. Reaction of C is the slow step with the condition that $[C]_o \gg [Br_2]_o$.

$$C + Br_2 \xrightarrow{k_4} D$$

$$C + Br_2 \xrightarrow{k_5} E$$

$$D + Br_2 \xrightarrow{k_7} F$$

$$E + Br_2 \xrightarrow{k_6} F$$

The rate law is:

$$-([Br_2]') = (k_4 + k_5)[C][Br_2] + k_7[D][Br_2] + k_6[E][Br_2] \quad \ldots\ldots \quad 3.9$$

A steady state assumption on D and E (i.e. for $[D] = \{k_4/k_7\}[C]$ and $[E] = \{k_5/k_6\}[C]$, equations 3.4 and 3.5 above), gives a rate law:

$$-([Br_2]') = 2(k_4 + k_5)[C][Br_2] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad 3.10$$

Thus, k_2^{obsd} is twice greater than the actual value $(k_4 + k_5)$.

The kinetics for phenol under consecutive second-order analysis

(i.e. $3[A]_o = [Br_2]_o$) has a varying rate profile depending upon the reactive species in the rate-determining step. For reaction via its phenoxide, the limiting rate constant is $(k_1 + k_2)$ for $5.3 < pH < 7$ (Figure 28). In the region $2.5 < pH < 5.3$, the slow step is bromination via 4-bromophenoxide, and the consecutive second-order rate constant gives the value of k_3.* For the region $1 < pH < 2.5$ the limiting rate constant ought to be k_7, which is the reaction constant for bromination of 2,4-dibromophenol, as determined from computer simulations at pH 1 using the observed monobromo product ratio for the appropriate partion of k_1/k_2. However, as explained earlier, the experimental results in this pH region may be in error since the reaction was not followed for long enough (see earlier discussion).

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* This value was also obtained by treating 4-bromophenol with two moles of bromine in this pH range (see Figure 28).