s-Triazines. Part V.[1] Synthesis and Hydrolytic Stability of 2,4-Dihalogeno-6-heteroaryl-*s*-triazines

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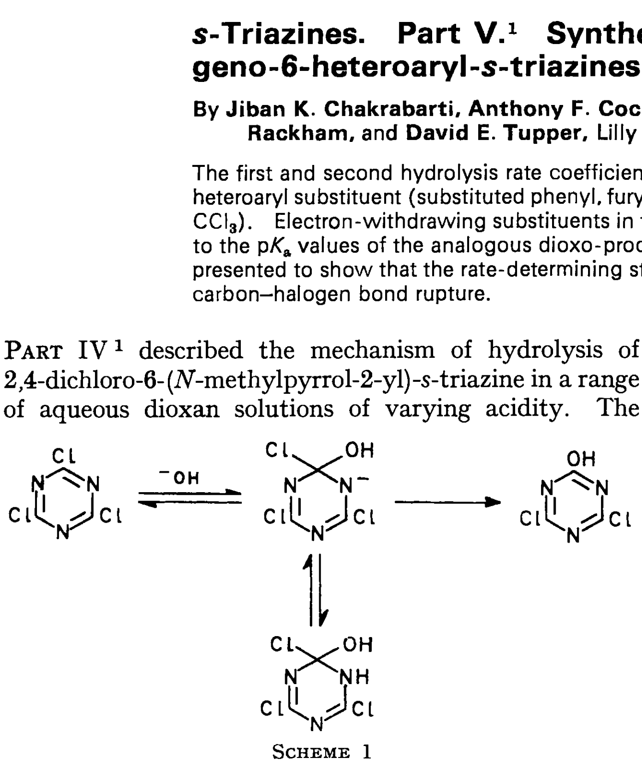
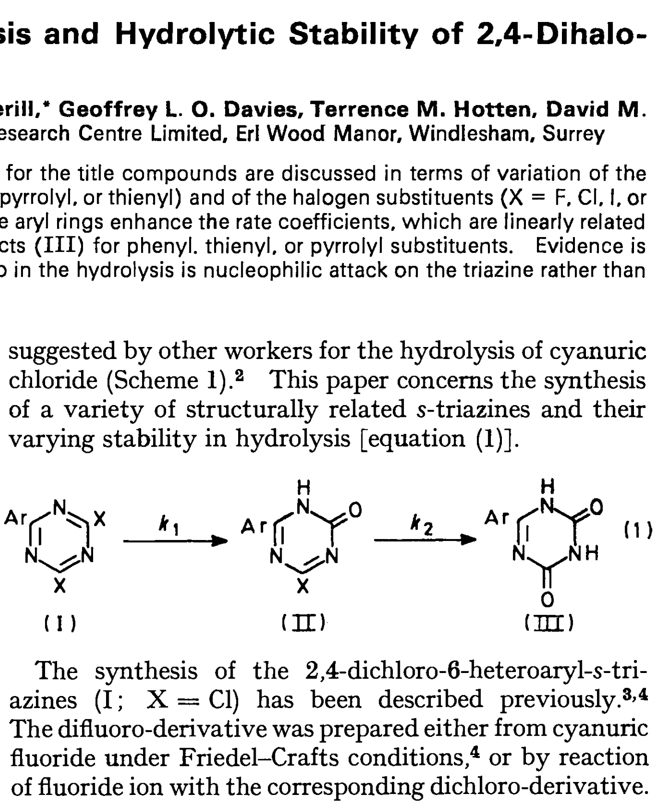
The first and second hydrolysis rate coefficients for the title compounds are discussed in terms of variation of the heteroaryl substituent (substituted phenyl, furyl, pyrrolyl, or thienyl) and of the halogen substituents (X = F, Cl, I, or CCl_3). Electron-withdrawing substituents in the aryl rings enhance the rate coefficients, which are linearly related to the pK_a values of the analogous dioxo-products (III) for phenyl, thienyl, or pyrrolyl substituents. Evidence is presented to show that the rate-determining step in the hydrolysis is nucleophilic attack on the triazine rather than carbon–halogen bond rupture.

PART IV[1] described the mechanism of hydrolysis of 2,4-dichloro-6-(*N*-methylpyrrol-2-yl)-*s*-triazine in a range of aqueous dioxan solutions of varying acidity. The kinetics for the initial hydrolysis in alkaline media did not require the intermediacy of a hydrate, as has been suggested by other workers for the hydrolysis of cyanuric chloride (Scheme 1).[2] This paper concerns the synthesis of a variety of structurally related *s*-triazines and their varying stability in hydrolysis [equation (1)].



SCHEME 1



The synthesis of the 2,4-dichloro-6-heteroaryl-*s*-triazines (I; X = Cl) has been described previously.[3,4] The difluoro-derivative was prepared either from cyanuric fluoride under Friedel–Crafts conditions,[4] or by reaction of fluoride ion with the corresponding dichloro-derivative. The latter method may give mixed halogeno-derivatives,

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[1] Part IV, A. F. Cockerill, G. L. O. Davies, and D. M. Rackham, *J.C.S. Perkin II*, 1974, 723.

[2] P. Rys, A. Schmitz, and H. Zollinger, *Helv. Chim. Acta*, 1971, **54**, 163.

[3] J. K. Chakrabarti, R. W. Goulding, and A. Todd, *J.C.S. Perkin I*, 1973, 2499.

[4] J. K. Chakrabarti and Tupper, submitted for publication in *J. Heterocyclic Chem.*

as was also found in the synthesis of the iodides by the same procedure. Surprisingly, bromide ion did not cause nucleophilic displacement [4] with the 2,4-dichloro-6-(*N*-methylpyrrol-2-yl)-*s*-triazine under the conditions used successfully for the other halides, and 2,4-dibromo-6-thienyl-*s*-triazine was therefore prepared by bromination of the corresponding dioxo-derivative (III; Ar = 2-thienyl). The bistrichloromethyl derivatives were prepared by the method described by Grundman *et al.* for 2-phenyl-4,6-bistrichloromethyl-*s*-triazine.[5]

EXPERIMENTAL

Preparation of Materials.—All samples had satisfactory spectral characteristics.

(a) 2,4-*Di-iodo*-6-(N-*methylpyrrol*-2-*yl*)-s-*triazine*. 2,4-Dichloro-6-(*N*-methylpyrrol-2-yl)-*s*-triazine (2·3 g, 0·01 mol) and sodium iodide (dried at 100° *in vacuo*; 9·0 g, 0·06 mol) were heated under reflux for 72 h in isobutyl methyl ketone (50 ml). Following hot filtration, the solution was allowed to cool, when the *di-iodo-compound* (1·9 g, 46%) crystallised, m.p. 180° (from methylene chloride–hexane), $\lambda_{max.}$ 344 nm (log ε 4·56) (Found: C, 23·5; H, 1·45; N, 13·6. $C_8H_6I_2N_4$ requires C, 23·3; H, 1·45; N, 13·6%).

In a similar experiment with 2 equiv. of sodium iodide for 20 h, a crude yellow solid was isolated, which showed no i.r. carbonyl absorption, but exhibited three *N*-methyl signals in the n.m.r. spectrum. Separation of the components was achieved by g.l.c. (2% XE 60; temperature programmed from 100 to 250° at 16° min^{-1}), the retention times being 4·4 (starting material), 5·95 (unknown), and 7·4 min (di-iodo-derivative) with a peak height ratio of 20 : 52 : 18. Thus it appears that the unknown peak is due to 2-chloro-4-iodo-6-(*N*-methylpyrrol-2-yl)-*s*-triazine.

(b) 2,4-*Difluoro*-6-(N-*methylpyrrol*-2-*yl*)-s-*triazine*. *N*-Methylpyrrole (0·81 g) and cyanuric fluoride (1·35 g) were stirred in dry benzene (20 ml) at 40° for 1 h, and left overnight at room temperature. After removal of solvent and recrystallisation of the residue from hexane, *product* (0·9 g, 46%) was obtained, m.p. 112·5—113°, $\lambda_{max.}$ 323 nm (log ε 4·19) (Found: C, 48·6; H, 3·1; N, 28·7. $C_8H_6F_2N_4$ requires C, 48·9; H, 3·1; N, 28·6%).

Alternatively, the difluoro-derivative was produced by nucleophilic displacement on the corresponding dichloro-*s*-triazine using an excess of potassium fluoride in boiling isobutyl methyl ketone. The crude product was contaminated with starting material and another component (g.l.c.), which elemental analysis indicates is 2-chloro-4-fluoro-6-(*N*-methylpyrrol-2-yl)-*s*-triazine.

(c) 2-*Heteroaryl*-4,6-*bistrichloromethyl*-s-*triazines*. Dry hydrogen chloride was passed into a mixture of trichloroacetonitrile (4·3 g, 0·03 mol) and thiophen-2-carbonitrile (1·6 g, 0·015 mol) cooled in ice for 2 h. After being left overnight at ambient temperature, the mixture was evaporated under reduced pressure over potassium hydroxide, and the white residue was recrystallised from ethanol to give 2-(2-*thienyl*)-4,6-*bistrichloromethyl*-s-*triazine* (1·7 g, 28%), m.p. 98—99° (Found: C, 27·1: H, 0·8; Cl, 53·2; N, 10·5; S, 8·0. $C_9H_3Cl_6N_3S$ requires C, 27·2; H, 0·75; Cl, 53·5; N, 10·5; S, 8·05%).

A similar procedure with *N*-methylpyrrole-2-carbonitrile,[6] gave 2-(N-*methylpyrrol*-2-*yl*)-4,6-*bistrichloromethyl*-s-*triazine* (24%), m.p. 141° (EtOH) (Found: C, 30·5; H, 1·5; Cl, 53·6; N, 14·1. $C_{10}H_6Cl_6N_4$ requires C, 30·5; H, 1·55; Cl, 53·9; N, 14·2%).

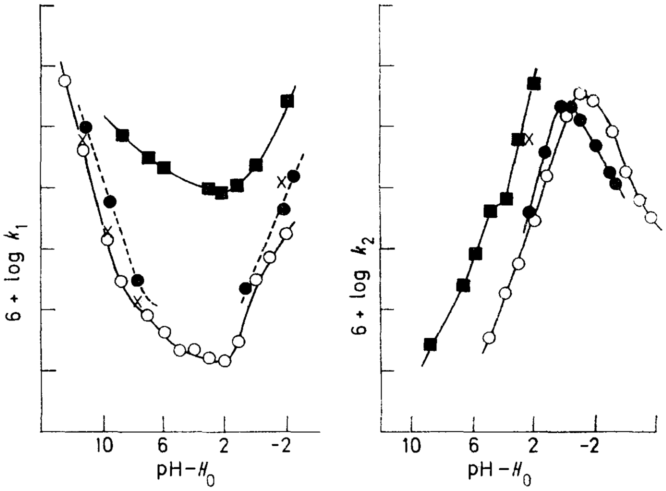

FIGURE 1 Leaving-group effects on the rates of hydrolysis of 2,4-dihalogeno-6-(*N*-methylpyrrol-2-yl)-*s*-triazines (I; Ar = *N*-methylpyrrol-2-yl) in buffered 20% dioxan–water at 30° (k_1, k_2 in s^{-1}): X = ■ F; ○ Cl; ● I; and × CCl_3

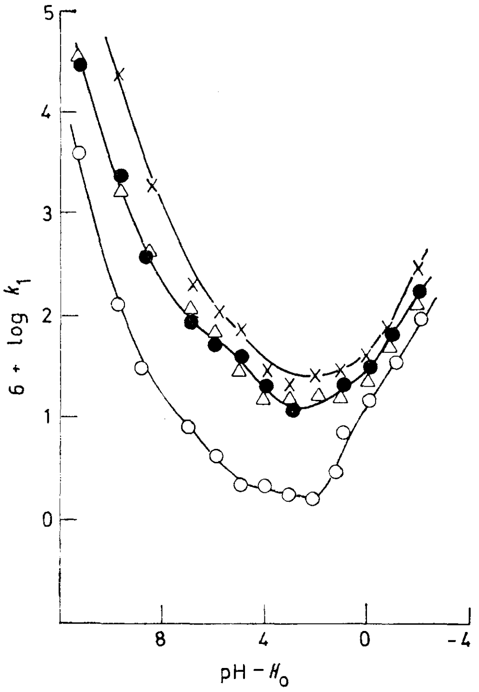

FIGURE 2 Influence of aryl group on the hydrolysis of 2-aryl-4,6-dichloro-*s*-triazines (I) in buffered 20% dioxan–water at 30° (k_1 in s^{-1}): Ar = △ Ph; ● 2-thienyl; × 2-furyl; and ○ *N*-methylpyrrol-2-yl

(d) 2,4-*Dibromo*-6-(2-*thienyl*)-s-*triazine*. A mixture of 6-(2-thienyl)-*s*-triazine-2,4-dione [3] (2·9 g, 0·015 mol), PBr_3 (9 g, 0·033 mol), Br_2 (5·3 g, 0·033 mol), and $POBr_3$ (26 g, 0·09 mol), was heated under reflux for 24 h with stirring. The cooled solution was poured onto ice and the solid was filtered off and dried *in vacuo* ($CaCl_2$). The dried powder was extracted with ether, removal of which left a yellow powder (3·6 g), which was fractionally crystallised

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[5] C. Grundman, G. Weisse, and S. Seide, *Annalen*, 1952, **577**, 77.

[6] J. K. Chakrabarti and T. M. Hotten, *J.C.S. Chem. Comm.*, 1972, 1226.

from carbon tetrachloride–light petroleum to give the *dibromo-derivative*, m.p. 187° (Found: C, 26·1; H, 1·0; Br, 49·9; N, 13·3; S, 10·1. $C_7H_3Br_2N_3S$ requires C, 26·2; H, 0·95; Br, 49·8; N, 13·1; S, 9·9%).

Kinetic Studies.—(a) *Hydrolysis rates*. The rates of hydrolysis of the various *s*-triazines were measured by u.v. spectroscopy in 20% (v/v) dioxan–water by the method described in Part IV.[1] For most substrates, replacement of the first halogen only was monitored over a narrow range of weakly alkaline media (pH 6—12; Table 1). More complete rate–pH profiles for the first and second halogen displacements for the series of 2,4-dihalogeno-6-(*N*-methylpyrrol-2-yl)-*s*-triazines are illustrated in Figure 1, while Figure 2 shows the influence of aryl substituents on the rate of the initial chlorine displacement.

TABLE 1

Rate coefficients for displacement at 30° of the first chlorine from some *s*-triazines in 20% dioxan–water containing buffer, and pK_a values of the corresponding dioxo-derivatives

	pH	12·3	11·3	9·6	8·65	6·9	5·9		pK_a [b]
	Compound (I; X = Cl)								
No.	Ar	10^2k/s^{-1} [a]	10^3k/s^{-1}	10^4k/s^{-1}	10^5k/s^{-1}	10^6k/s^{-1}	10^6k/s^{-1}	(III)	(III, H+)
1	Pyrrol-2-yl	7·67	6·75						
2	*N*-Phenylpyrrol-2-yl	8·84	8·80	4·52	12·4			5·5	~−1
3	*N*-methylpyrrol-2-yl	5·98	4·24	1·43	2·87	7·91	3·08	6·7	−1·25
4	*N*-Methyl-4-nitropyrrol-2-yl		50·4	30·0	53·6			4·7	−2·9
5	3-Thienyl		36·4	18	31·1			5·0	−1·1
6	4-Nitro-2-thienyl		155	78·7	156	575		3·95	<−3
7	5-Acetyl-2-thienyl			111	149			4·1	<−3
8	5-Bromo-2-thienyl		59·2	32·4	45·3			4·4	−2·4
9	4-Methyl-2-thienyl			26·7	30·4			4·8	−1·0
10	5-Ethyl-2-thienyl		22·1	11·1	29·7			4·9	−1·4
11	5-Methoxy-2-thienyl	12·4	9·5	9·7	16·9	26·6	14·7	5·0	−1·6
12	2-Thienyl		30·3	22·5	43·3	93	54·8	4·7	−1·8
13	2-Furyl			242	195	210	117	5·7	~−1
14	5-Nitro-2-furyl				380			5·2	
15	Phenyl		32·9	17·7	42·8	126	74·8		
16	3-Nitrophenyl				115				

[a] Error in rate coefficients ±2—3%. [b] ±0·2 pK units.

TABLE 2

Element effects on hydrolysis rates of (I; Ar = *N*-methylpyrrol-2-yl) and pK_a values of (III; Ar = *N*-methylpyrrol-2-yl)

	$k_1^X : k_1^{Cl}$ at pH						pK_a [c]	$k_2^X : k_2^{Cl}$ at pH		
X	8	6	4	2	0	−2		5	3	1
F	380	520	570	560	90	125	5·55	100	50	160
Cl	1	1	1	1	1	1	5·20 ± 0·03	1	1	1
I	3·5				1·9	4·4	5·45			2·5
CCl_3	1·2					10·6 [a]	5·80		30·3 [b]	

[a] At H_0 −1·85. [b] At pH 2·37. [c] ±0·05 pK units.

(b) *Reaction products*. The products of hydrolysis [(II) and (III)] of the various substituted *s*-triazines (I) were not isolated, but were identified in solution by spectral characteristics analogous to those of the well characterised corresponding monochloro- and dioxo-derivatives which are formed in the hydrolysis of 2,4-dichloro-6-(*N*-methylpyrrol-2-yl)-*s*-triazine.[1] Alkaline solutions of monohalogeno-derivatives (II) were prepared as described previously.[1]

(c) pK_a *Determinations*. The pK_a values of the dioxo-derivatives (III) and their conjugate acids were calculated, where possible, from u.v. absorption measurements of completely reacted solutions of the corresponding *s*-triazine derivatives (I) (see Table 1).[1] The pK_a values of the monohalogeno derivatives (II) are listed in Table 2.

DISCUSSION

Influence of the Aryl Substituent on the Displacement of the First Chlorine in the s-*Triazines*.—The shape of the rate–pH profile for the hydrolysis of the first chlorine for a number of 2-aryl-4,6-dichloro-*s*-triazines is similar to that reported previously for the hydrolysis of the 2-*N*-methylpyrrolyl derivative (Figure 2).[1] The decrease in rate coefficients as the pH decreases accords with a change in nucleophile from hydroxide ion to the less reactive buffer anions, with the minimum at pH *ca.* 2, reflecting the attack of water on the triazine. With increasing acidity, the rate rises as the pK_a of the substrate is approached,[1] the rate-determining step involving attack of water on the conjugate acid. In acidic solution, all four aryl derivatives (Figure 2) have similar stability, the pyrrole derivative being the most sensitive towards acid catalysis in the pH region of our studies. However, in the neutral range, the pyrrole derivative is an order of magnitude less reactive as a result of its greater electron-releasing property.[7] Surprisingly, the reactivities of the other three aryl derivatives are very similar, except in the more alkaline region.

The rate coefficients for the substituted 2-thienyl derivatives are correlated by the Hammett equation, the positive reaction constants clearly demonstrating that the hydrolysis is promoted by electron-withdrawing substituents (Table 3). The magnitude of our reaction constant is similar to that reported by Koopman for the

[7] A. F. Cockerill, M. F. Ellis, D. M. Rackham, and E. Wildsmith, *J.C.S. Perkin II*, 1973, 173.

TABLE 3

Linear free energy relationships in hydrolysis of dichloro-*s*-triazines

Correlation [a]	pH	*s* [b]	*r* [c]	Compounds [d]
1 $\log k_1 = 1{\cdot}16\sigma - 1{\cdot}55$	11·3	0·102	0·975	6, 8, 9, 10, 11, 12
2 $\log k_1 = 0{\cdot}96\sigma - 2{\cdot}74$	9·6	0·065	0·988	6, 8, 10, 11, 12
3 $\log k_1 = 1{\cdot}01\sigma - 3{\cdot}42$	8·7	0·063	0·990	6, 7, 9, 10, 11, 12
4 $\log k_1 = 0{\cdot}66pK_a - 0{\cdot}24$	8·7	0·137	0·964	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16

[a] k_1/s^{-1} Values refer to rate of hydrolysis of the first chlorine from the 2-aryl-4,6-dichloro-*s*-triazines in 20% dioxan–water at the pH values shown. Results 1–3 concern substituted 2-thienyl derivatives. Correlation 4 relates rate coefficient to the pK_a value of the corresponding dioxo-compound (*cf.* Figure 3). [b] Standard deviation in slope. [c] Correlation coefficient. [d] Numbers refer to compounds in Table 1.

hydrolysis of 2-aryl-4,6-dichloro-*s*-triazines in aqueous acetone.[8]

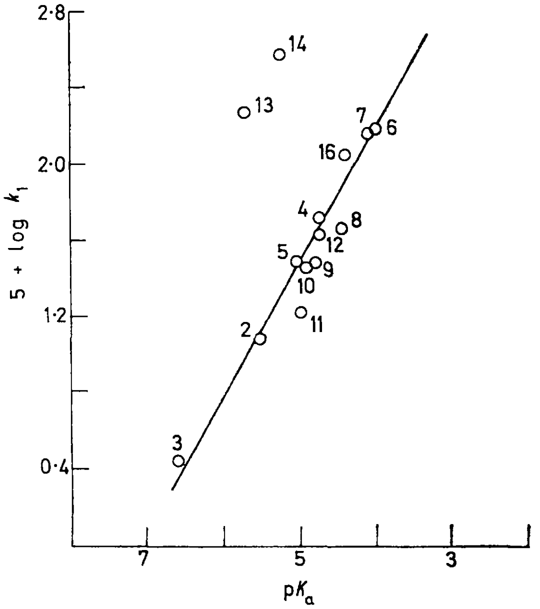
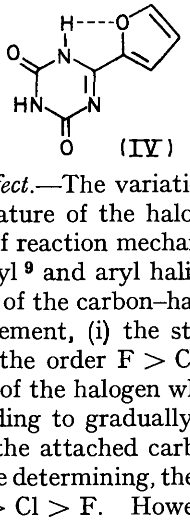


FIGURE 3 Correlation of hydrolysis coefficient (k_1/s^{-1}) for 2-aryl-4,6-dichloro-*s*-triazines in 20% dioxan–water (pH 8·65) at 30° against pK_a values of the corresponding 6-aryl-*s*-triazine-2-4-diones. Numbers refer to compounds as listed in Table 1

The specific rates of alkaline hydrolyses of the substituted thienyl- and pyrrolyl-dichloro-*s*-triazines are linearly related to the pK_a values of the corresponding dioxo-compounds (Table 3, result 4; Figure 3), the rate increasing with the electron-withdrawing power of the aryl group. However, the furyl derivatives are hydrolysed more rapidly than is suggested from the correlation involving their pK_a values. This deviation could be attributed to hydrogen bonding depressing the acid dissociation [see (IV)], but not operating in the transition state for hydrolysis of the dichloro-*s*-triazines. This kind of hydrogen-bonding interaction should be less important in the *N*-substituted-pyrrolyl and thienyl-substituted dioxo-compounds because of steric and weaker electronic interactions respectively.


(IV)

Leaving-group Effect.—The variation in the rate coefficient with the nature of the halogen has often been used as a criterion of reaction mechanism in nucleophilic substitutions of vinyl[9] and aryl halides.[10] Two factors affect the reactivity of the carbon–halogen bond towards nucleophilic displacement, (i) the strength of the bond which decreases in the order F > Cl > Br > I and (ii) the inductive effect of the halogen which decreases along the same series leading to gradually decreasing electrophilic character of the attached carbon atom. Thus, if bond breaking is rate determining, the reactivity sequence should be I > Br > Cl > F. However, if bond formation is rate determining, the reactivity sequence should be F $\gg$ Cl $\sim$ Br $\sim$ I, as in this case, and the inductive factor dominates for the reactivity of the fluoro-compound, but balances out with the bond strength factor for the other halogens because of the partial bond weakening, which occurs with the hybridisation change from sp^2 to sp^3 in attaining the transition state. Thus, the relative reactivity of the fluoro-derivative provides the critical mechanistic criterion.

The reactivities of our *s*-triazines for both the first and second displacements fit the sequence F $\gg$ Cl $\sim$ I in accordance with bond formation being rate determining for both nucleophilic displacements (see Figure 1 and Table 2). However, the direct rate constant comparisons for both processes at a given acidity are not without complications. For the initial halogen displacement, the influence of the second halogen has to be considered, and for the second displacement, allowance has to be made for the varying concentrations of protonated, neutral, and anionic forms of the monohalogeno-derivatives (II). Both these problems can be solved with a knowledge of the pK_a values of the monohalogeno-derivatives (II) (see Table 2).

Our pK_a values for the monohalogeno-derivatives (II) indicate the following order of increasing electron-withdrawing power; CCl_3 < F < I < Cl, typical of halogen substituents in aryl rather than alkyl systems. Allowing for the slight electron-releasing character of fluorine relative to chlorine leads to an increase in the magnitude of the $k_{1(F)} : k_{1(Cl)}$ ratios listed in Table 2 for studies at alkaline and neutral pH. However, for acidic solutions, in the absence of a knowledge of the pK_a values of the conjugate acids of the *s*-triazines, the $k_F : k_{Cl}$ are a matter of conjecture. The narrowing of the separation between the profiles (Figure 1) suggests the dichloro-derivative is protonated in slightly less acidic media. Thus, allowance for this apparent dif-

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[8] H. Koopman, *Rec. Trav. chim.*, 1962, **81**, 465.

[9] (*a*) Z. Rappoport, *Adv. Phys. Org. Chem.*, 1969, **7**, 1; (*b*) Z. Rappoport and A. Topol, *J.C.S. Perkin II*, 1972, 1823.

[10] J. F. Bunnett, E. W. Garbisch, jun., and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 5967.

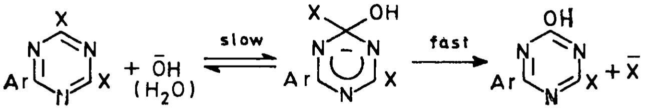
ference in pK_a would lead to increased $k_F : k_{Cl}$ ratios. The more shallow increase in rate with increasing pH for the difluoro-derivative suggests, as might be expected, that this substrate is less selective towards attack by the different nucleophiles.

The anionic forms of (II) are very unreactive towards hydrolysis.[1] The rise in k_2 with increasing acidity reflects an increase in the concentration of (II) and eventually of its conjugate acid. The rate attains a maximum near the pK_a for the latter species, and further increased acidity leads to a fall in rate as the water activity declines. For the chloro-compound, the two pK_a values are spaced fortuitously to produce a linear increase in the rate coefficient over the entire pH region from 6 to 0. However, for the fluoro-derivative a distinct discontinuity is apparent, implying that the two pK_a values are more separated. This suggests the pK_a of the latter conjugate acid lies between −1 and −2, and is supported by the fact that hydrolysis studies in the acid region pH-H_0 1 to −2 were precluded, the reaction being complete inside 10 s.

In the absence of a knowledge of the exact contribution of the individual buffers to the observed rate coefficient, it is difficult to predict the $k_F : k_{Cl}$ ratios in the pH region 6—3 for nucleophilic attack on the uncharged monohalogenotriazines. However, at pH 1, buffers were not used, and the dominant process is clearly attack of water on the protonated monohalogenotriazines. Thus, assuming pK_a values of 0, −1, and −1 to −2 for the iodo-, chloro-, and fluoro-conjugate acids (II), and a water activity of 45·5 mol l^{-1}, the following rate coefficients can be estimated: $k_2^{H_2O}$ (conjugate acid)/l mol^{-1} s^{-1} = $1{\cdot}3 \times 10^{-3}$ for (II; X = I); 5×10^{-3} for (II; X = Cl); and 8×10^{-1}—8 for (II; X = F). This gives a $k_{Cl} : k_I$ ratio of 4 and a $k_F : k_{Cl}$ ratio between 160 and 1600, in agreement with rate-determining nucleophilic attack.

Brief comment is warranted on the relative reactivity of the trichloromethyl derivative (I; X = CCl_3). In alkaline solution, values of k_1 are similar to those of the chloro-compound. The pK_a of (II; X = CCl_3) is slightly greater than that of the other halogen derivatives (Table 2), suggesting that the trichloromethyl group is slightly more electron releasing than the halogen substituents. This fact is confirmed in acidic solution as k_1 values exceed those for the iodo- and chloro-compounds, and k_2 values approach those for the fluoro-derivative (Figure 1).

Conclusions.—The large $k_F : k_{Cl}$ ratios and similar values of k_{Cl} and k_I,* the rate acceleration by electron-withdrawing aryl substituents, and the observation of excellent pseudo-first-order kinetics and well defined isosbestic points for both conversions (I) ⟶ (II) and (II) ⟶ (III) prompts us to propose rate-determining nucleophilic attack on the triazine and its monohydroxy-derivative under our reaction conditions (Scheme 2).



SCHEME 2 X = halogen

Our kinetic results do not require a mechanism involving formation of an intermediate hydrate as has been proposed for the hydrolysis of cyanuric chloride in alkaline aqueous acetone (see Scheme 1).[2]

[3/2492 *Received, 6th December,* 1973]

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* A limited number of experiments with 2,4-dihalogeno-6-(2-thienyl)-*s*-triazines showed the dibromo- and dichloro-derivatives were of similar reactivity in the first stage of hydrolysis.