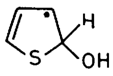
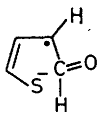
Electron Spin Resonance Studies. Part 59.[1] Radical Reactions of Thiophens: the Formation and Reactions of Some Sulphur-conjugated Radical-cations

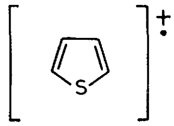
By **Bruce C. Gilbert,* Richard O. C. Norman,** and **Peter S. Williams,** Department of Chemistry, University of York, Heslington, York YO1 5DD

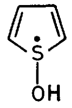
E.s.r. spectroscopy has been employed to study the mechanisms of reaction of thiophen and several of its derivatives with a variety of radicals (·OH, $Cl_2^{-\cdot}$, $NH_3^{+\cdot}$, and $SO_4^{-\cdot}$) as a function of pH. The radicals detected are mainly hydroxy-adducts but also include 2-thenyl, formed from 2-methylthiophen and 2-thenylacetic acid under certain circumstances, and thenoxyl radicals. Evidence is presented that radical-cations are involved in many of the reactions; with $Cl_2^{-\cdot}$ and $SO_4^{-\cdot}$ they are formed directly, whereas in the reaction with ·OH they are formed only at low pH, *via* acid-catalysed elimination of OH^- from the first-formed hydroxy-adducts. Although the radical-cations are normally readily hydrated, other fates, including deprotonation and decarboxylation, have been identified. Comparisons between the results obtained for ·OH and for $Cl_2^{-\cdot}$ with certain substrates enable the regioselectivities of both ·OH addition and radical-cation hydration to be determined.

THERE has been considerable interest in the reactions of radicals (especially those produced radiolytically) with aromatic substrates [2] and e.s.r. spectroscopy has proved a useful tool for studying the mechanisms of such processes.[3] Relatively little work on thiophen and its derivatives has been carried out, although we note that both u.v. spectroscopic [4,5] and product studies [5] indicate that reaction of thiophen with radiolytically produced hydroxyl radicals leads to the formation of the adduct (1) which, at high pH, undergoes ring-opening to give (2).


(1)


(2)


(3)


(4)

We have previously shown [1] that a variety of enol ethers can be oxidized to the corresponding radical-cations, either directly (with $Cl_2^{-\cdot}$) or *via* an addition–elimination sequence with ·OH at low pH. We here report the results of a further e.s.r. study designed to discover the modes of reaction of a variety of radicals (·OH, $Cl_2^{-\cdot}$, $SO_4^{-\cdot}$, and $NH_3^{+\cdot}$) with thiophen and some derivatives which are likewise electron-rich. We were particularly interested to investigate the importance of direct electron transfer, to give *e.g.* (3), and of the characteristics of such species, if formed, and also of the possible formation of radicals *via* attack at sulphur rather than at the ring positions; thus analogy with results obtained for reaction of [6] ·OH and [7] $NH_3^{+\cdot}$ with dialkyl sulphides would suggest that adducts of the type (4) might be involved.

RESULTS AND DISCUSSION

Reactions were carried out in the cavity of an e.s.r. spectrometer with a continuous three-way flow mixing system and a ' mixing time ' (the time between mixing and observation) of *ca.* 80 ms. The hydroxyl radical, sulphate radical-anion, and ammoniumyl radical-cation were generated by reaction of titanium(III) ion with hydrogen peroxide,[1] sodium peroxydisulphate,[1] and hydroxylamine hydrochloride,[7] respectively [reactions (1)—(3)] with, for pH > 2.5, the addition of the disodium salt of ethylenediaminetetra-acetic acid (edta) as a sequestering agent for Ti^{III}. The chlorine radical-anion was generated by reaction of Cl^- (added as 1 mol dm^{-3} NaCl) with either ·OH (at pH < 2.5) or $SO_4^{-\cdot}$ (at pH > 3.0), as described previously [1] [see reactions (4)—(6)].

$$Ti^{III} + H_2O_2 \longrightarrow Ti^{IV} + \cdot OH + OH^- \qquad (1)$$

$$Ti^{III} + S_2O_8^{2-} \longrightarrow Ti^{IV} + SO_4^{-\cdot} + SO_4^{2-} \qquad (2)$$

$$Ti^{III} + NH_4OH \longrightarrow Ti^{IV} + H_2O + NH_3^{+\cdot} \qquad (3)$$

$$\cdot OH + Cl^- \longrightarrow HOCl^{-\cdot} \xrightarrow{H^+} H_2O + Cl\cdot \qquad (4)$$

$$SO_4^{-\cdot} + Cl^- \longrightarrow SO_4^{2-} + Cl\cdot \qquad (5)$$

$$Cl\cdot + Cl^- \longrightarrow Cl_2^{-\cdot} \qquad (6)$$

(a) *Reactions of Thiophen.*—(i) *Results.* When thiophen (0.007 mol dm^{-3})† was oxidised by ·OH at pH *ca.* 6.0, two radicals were detected. They were characterized as the 2- and 3-hydroxy-adducts [structures (1) and (5), respectively; see Figure 1a and Table], with *g*-factors and splittings as indicated. For (1), the parameters are as expected for an allyl-type radical with some delocalization of the unpaired electron onto sulphur and with a large splitting (reflecting effective hyperconjugative interaction) from the cyclohexadienyl-type β-

---

† All concentrations referred to in the text are those after mixing.

proton at the point of attack. The radical (5) has an α-proton coupling and *g*-value typical of an α-thioalkyl radical and the β-proton splitting is again large, as anticipated; there is evidently very little effective delocalization of the unpaired electron across sulphur into the double bond. {One point of detail concerning the assignment of (5) should be noted. The two small doublet splittings of 0.20 and 0.06 mT evidently arise from interactions with the protons on the 4-position and on oxygen, respectively; the possibility that either arises

E.s.r. parameters of radicals formed in the reactions of thiophen and its derivatives (hyperfine splittings in mT) [b]

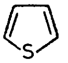
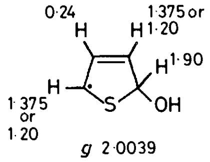
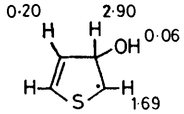
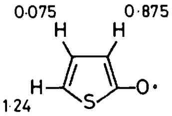
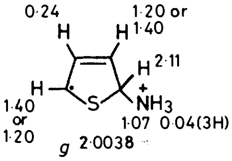
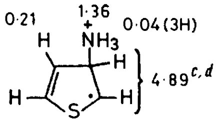
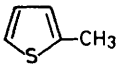
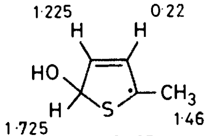
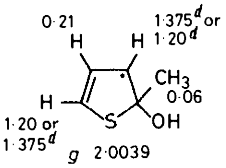
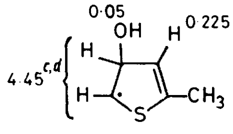
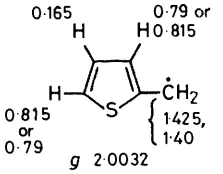
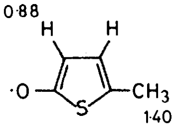
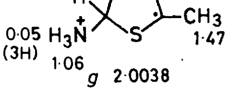
<table>
<tr><th>Substrate [a]</th><th>Attacking species</th><th></th><th></th><th></th></tr>
<tr><td></td><td>•OH</td><td>
g 2·0039
(1)</td><td>$^{-}S—CH{=}CH—\dot{C}H—CH{=}O$
a 0·52(2H), 0·425(2H)
g 2·0046
(2)</td><td>
g 2·0038
(5)</td></tr>
<tr><td></td><td></td><td>
g 2·0037
(6)</td><td>$O{=}\dot{S}—CH{=}CH—CH{=}CH—O^{-}$
a 0·75(1H), 0·575(1H), 0·23(1H)
g 2·0090
(7)</td><td></td></tr>
<tr><td></td><td>$Cl_2^{\cdot-}$</td><td>(1), (6)</td><td></td><td></td></tr>
<tr><td></td><td>$NH_3^{+\cdot}$</td><td>
(8)</td><td>
g 2·0039
(9)</td><td></td></tr>
<tr><td></td><td>·OH</td><td>
g 2·0037
(10)</td><td>
g 2·0039
(11)</td><td>
g 2·0039
(12)</td></tr>
<tr><td></td><td></td><td>
g 2·0032
(13)</td><td>
g 2·0036
(14)</td><td></td></tr>
<tr><td></td><td>$Cl_2^{\cdot-}$</td><td>(10), (13), (14)</td><td></td><td></td></tr>
<tr><td></td><td>$NH_3^{+\cdot}$</td><td>
(15)</td><td></td><td></td></tr>
</table>

TABLE (*continued*)

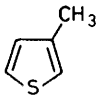
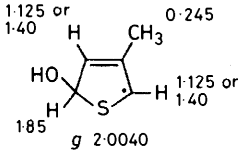
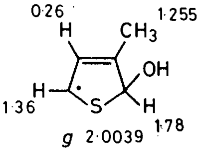
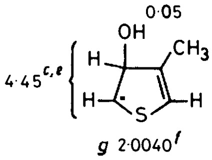
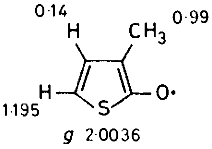
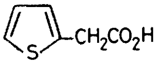
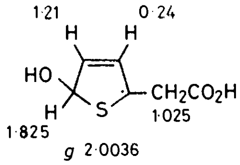
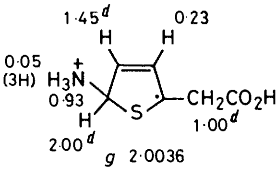
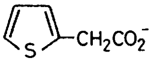
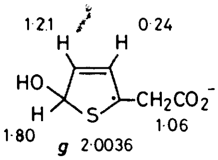
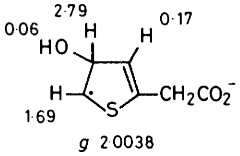
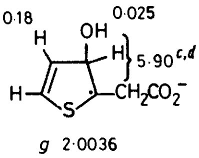
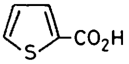
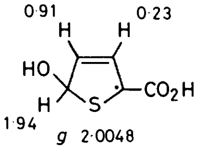
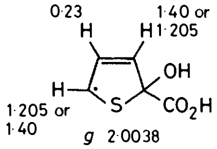
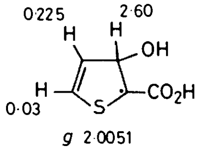
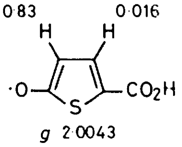
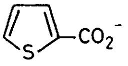
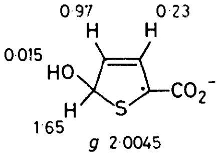
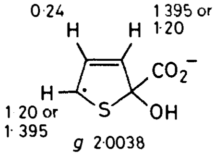
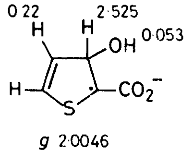
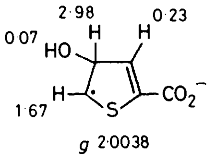
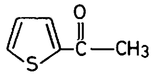
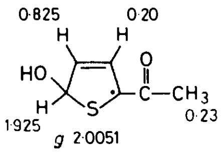
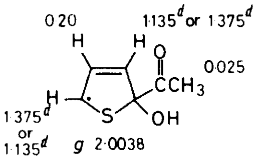
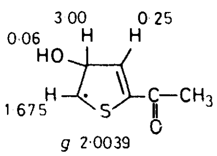
Substrate[a]	Attacking species			
	·OH	 (17)	 (18)	 (19)
		 (20)		
	$Cl_2^{\cdot-}$	(18), (20)		
	·OH	 (23)	(13)	
	$Cl_2^{\cdot-}$	(13)		
	$NH_3^{\cdot+}$	 (24)		
	·OH	 (25) (13)	 (26)	 (27)

TABLE (*continued*)

Substrate [a]	Attacking species	
	·OH	 (29)  (30)  (31)  (32)
	$Cl_2^{\cdot-}$	(29),(30), (32)
	·OH	 (33)  (34)  (35)  (36)
	$SO_4^{\cdot-}$	(33)
	·OH	 (37) (40)  (38)  (39)
	$Cl_2^{\cdot-}$	(37)

[a] For conditions, see text. [b] Splittings ±0.01 mT, *g* ± 0.0001 unless indicated otherwise. [c] Sum of splittings; separate values not determined (see text). [d] ±0.025 mT. [e] ±0.05 mT. [f] ±0.0002.

from an interaction with 5-H is ruled out by our observation of similar splittings for analogous radicals where this position is substituted [see, *e.g.* (26) in the Table].}

The relative concentrations of radicals (1) and (5) remained constant (*ca.* 4 : 1) in the pH range 4.5—6. As the pH was lowered below 4.5, however, the signal from (5) was reduced in intensity and a corresponding increase in [(1)] was observed; by pH 2.5, only the latter could be detected.

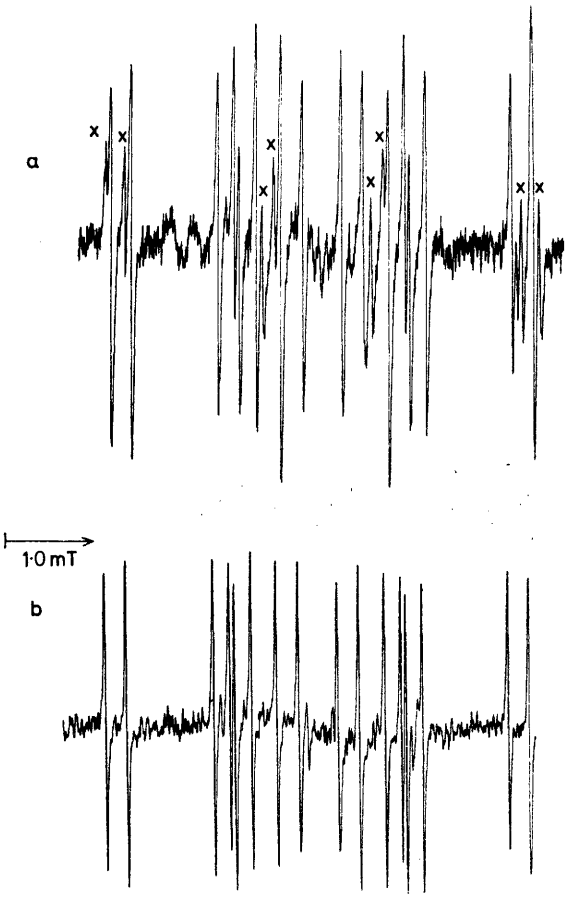
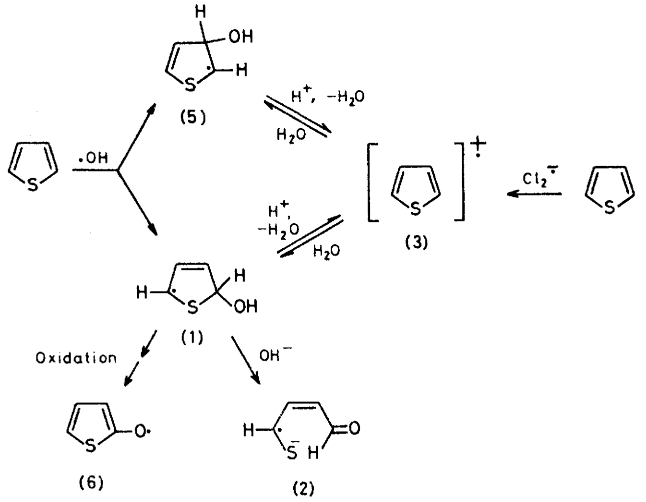


FIGURE 1 (*a*) E.s.r. spectra of (1) and (5) (the absorptions from which are indicated ×) obtained from the reaction between thiophen and •OH at pH 6.5. (*b*) E.s.r. spectra from (1) and, in trace amounts, (6), obtained from the reaction between thiophen and •OH at pH 1.5

The major species detected when thiophen was oxidised by $Cl_2^{-\cdot}$ below pH 2.5 was also the 2-hydroxy-adduct (1) (no signals were obtained from the $SO_4^{-\cdot}$–Cl^-–thiophen system at pH > 3, probably because of the facility of radical destruction by oxidation with $S_2O_8^{2-}$ under these conditions[8]); in addition, a signal assigned to the thenoxyl radical (6) was also detected. Our assignment here is based in part (see also later) on the finding that the radical is formed in a secondary reaction, since its concentration increased as the flow-rate was decreased (and also as the thiophen concentration was reduced), and also by comparison with the splittings for the related phenoxyl[9] and furan-2-oxyl radicals.[10] Signals from (6) were also detectable at pH < 2.0 during oxidation by the hydroxyl radical under conditions of low thiophen concentration and slower flow-rates, but [(6)] was significantly lower than in the corresponding reactions of $Cl_2^{-\cdot}$ (see Figure 1b).

When thiophen was oxidized by •OH at pH > 6 (again with [thiophen] 0.007 mol dm^{-3}) signals from (1) and (5) were again observed, together with signals from three other species. One of these, known[11] to result from reaction of •OH with edta, was prominent only above pH *ca.* 8; it will not concern us here. The remaining two appeared at the expense of (1) as the pH was raised above 6 until by pH 8.5 signals from (1) had disappeared completely. The first of these radicals is assigned the structure (2) on the basis of its splittings (which are similar to those[10] for the analogous radical-anion $^-$OCH=CH–$\dot{C}$H–CHO) and *g*-value. The second gave rise to a spectrum comprising eight broad lines, analysed in terms of three doublet splittings of 0.75, 0.575, and 0.23 mT, and *g* 2.009 0. The *g*-value is characteristic of a sulphinyl radical (*cf.* ArSO•) in which spin density has been removed into a adjacent π-system;[12] on the basis of this, and from mechanistic considerations (see later), we suggest that the spectrum is from the sulphinyl radical (7).

Reaction of thiophen with $NH_3^{+\cdot}$ at low pH led to the detection of signals from a mixture of two radicals, dominated by that assigned to the 2-adduct (8) on the basis of the allyl-type proton couplings and the splittings from the (β)-nitrogen and the three attached protons. The spectrum of a second radical, present in about one-quarter of the concentration of (8), had an overall width (*ca.* 7.9 mT) and small splittings of 0.21 (1 H) and 0.04 mT (3 H) which are as expected for the 3-adduct (9), though detailed analysis proved impossible. There was no trace of signals from ring-opened radicals or •OH adducts, and the ratio of [(8)] : [(9)] did not appear to vary with pH.

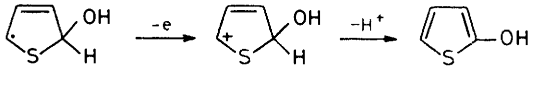


SCHEME

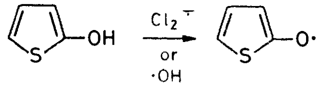
(ii) *Mechanistic implications.* The detection of radicals (1) and (5) during the reaction of •OH in the pH range 4—6 is consistent with the primary process being addition to the 2- and 3-positions (see Scheme). The predominance of (1) under these conditions presumably reflects the kinetic control of attack and results from the extra stability associated with the transition state leading to the allylic system. Our detection of both isomeric adducts is in contrast with the results of radiolysis experiments in which evidence for only the 2-adduct was obtained.[4,5] The disappearance of (5) as the pH was lowered has several analogies in the chemistry of both αβ-di-oxygen-substituted radicals[1] and hydroxyl-radical adducts of benzene and its derivatives[13] and is interpreted in terms of the increased importance of its rearrangement to (1) *via* acid-catalysed loss of OH^- to form the radical-cation (3) and subsequent rehydration. [Radical (1) may also form (3) in an analogous reaction, although this cannot be established here; the pH at which this would become important is expected to be less than that for (5); see later.] The results of the reaction with $Cl_2^{-\cdot}$, which evidently involves direct electron transfer, confirm that the preferred product of radical-cation hydration is indeed (1). However, at this stage it is impossible to conclude whether this reflects *thermodynamic* control of the interconversion of (1) and (5) (with rapid loss of OH^- from each) or the irreversibility of the reaction leading to (1). We were unable to generate the radical-cation directly (with $Cl_2^{-\cdot}$) at pH values high enough(> *ca.* 4.5) to ensure that the ratio of radicals is governed solely by the kinetic control of hydration. These distinctions are discussed further below.

Radical (6), detected with either $Cl_2^{-\cdot}$ or ·OH at low pH, evidently arises *via* reactions of a product of the primary process (such a product would presumably build up down the flow tube and would complete more effectively for $Cl_2^{-\cdot}$ at low thiophen concentrations). We envisage that this occurs *via* one-electron oxidation of radical (1) followed by deprotonation of the resulting carbonium ion and further oxidation [reactions (7) and (8)]. The feasibility of this route in the generation of the thenoxyl radical was investigated by adding Fe^{III} [as $K_3Fe(CN)_6$] to the reaction system, for this ion is known to be an effective radical oxidant in, for example, the quantitative conversion of hydroxycyclohexadienyl radicals to phenols.[14] In accord with our suggestion, the addition of 1 mmol dm^{-3} Fe^{III} to the $Cl_2^{-\cdot}$ oxidation resulted in the complete loss of the signal from (1) and a corresponding increase in the intensity of the signal from (6); and the addition of 4 mmol dm^{-3} Fe^{III} to the reaction with ·OH at pH 1.1 resulted in the almost complete conversion of (1) into (6). In the absence of Fe^{III}, it seems likely that the oxidant in reaction (7) is hydrogen peroxide (in both $Cl_2^{-\cdot}$ and ·OH systems), whereas in (8) the oxidants are $Cl_2^{-\cdot}$ and ·OH respectively.*

The detection of the open-chain species (2) at the expense of (1) in the reaction with ·OH at pH > 6 is in accord with previous suggestions[4] that the latter undergoes base-catalysed ring-opening (see Scheme). We suggest that the appearance of the sulphinyl species (7) is indicative of the occurrence of further molecular oxidation (*e.g.* by H_2O_2) and radical oxidation of (2) [*cf.* the ready conversion of thiols into sulphinyl radicals in the Ti^{III}–H_2O_2 system[15]] as shown in reactions (9) and (10).

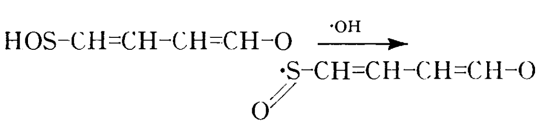


(1) (7)



(6) (8)

$$\text{S-CH=CH-}\dot{\text{C}}\text{H-CH=O} \longleftrightarrow \dot{\text{S}}\text{-CH=CH-CH=CH-O} \xrightarrow{H_2O_2} \text{HOS-CH=CH-CH=CH-O} \quad (9)$$



$$\text{HOS-CH=CH-CH=CH-O} \xrightarrow{\cdot OH} \underset{\displaystyle /\!\!/ O}{\cdot\text{S}}\text{-CH=CH-CH=CH-O} \quad (10)$$

We note that $NH_3^{+\cdot}$ apparently reacts with thiophen by direct addition to give the radicals (8) and (9), and that these show no tendency to undergo acid-induced fragmentation. The (kinetic) preference for the (stabilized) radical (8) parallels the selectivity of hydroxyl attack. It is interesting to note that $NH_3^{+\cdot}$ is evidently not capable of one-electron abstraction to generate a radical-cation, for otherwise OH adducts would have been detected; nor does it add at sulphur, as it apparently does in its reactions with sulphides,[7] sulphoxides,[7] and disulphides.[16] In this respect ·OH resembles $NH_3^{+\cdot}$ in preferring to add to the ring atoms in thiophen rather than to sulphur itself.

(b) *Reactions of 2-Methylthiophen.*—(i) *Results.* When 2-methylthiophen (0.003 mol dm^{-3}) was oxidized with ·OH in the pH range 2—7 the major species detected were the hydroxy-adducts (10) and (11), in a concentration ratio *ca.* 4 : 1; in addition, at pH > *ca.* 4, traces of signals tentatively attributed to a third adduct (12) were observed. The assignment of spectra follow from those presented previously. As the pH was lowered from 2 to 1.5, signals from (11) disappeared and the spectrum of a fourth species, identified as the thenyl radical (13), appeared (the parameters we observed are closely similar to those reported for this radical when it was generated from 2-methylthiophen by reaction with t-butoxyl[17]). Further lowering of the pH resulted both in an increase in [(13)] at the expense of [(10)] and in the detection of a weak signal attributed to the thenoxyl radical (14). The latter signal was significantly enhanced by the addition of 1 mmol dm^{-3} $K_3Fe(CN)_6$, when signals from (10) and (13) were removed completely. At

---

* The mechanisms of oxidation in reaction (8) probably involve direct electron transfer, for $Cl_2^{-\cdot}$ and addition–elimination, for ·OH; the necessity for acid catalysis in the latter would explain the fact that (6) was only detected at low pH.

pH < 0.3, signals from (10) were no longer detected (see Figure 2).

Reaction with $Cl_2^{-\cdot}$ in the pH range 0—2 resulted in the detection of moderately intense signals from the thenyl radical (13) and from (10), together with weak signals from (14), and an intense singlet (*g* 2.013 2) due to the Ti^{IV}–$HO_2\cdot$ complex (S_1). At pH 1.75 the ratio of [(13)] : [(10)] was *ca.* 2 : 1; as the pH was lowered to <1.0, the signal from (10) disappeared and that from (13) increased. Signals from (13) were removed by the addition of 1 mmol dm^{-3} $K_3Fe(CN)_6$, although under these conditions [(14)] was one-fifth that observed in the corresponding reaction with ·OH. As in experiments with thiophen, the use of $S_2O_8^{2-}$ at pH > 3 removed all signals.

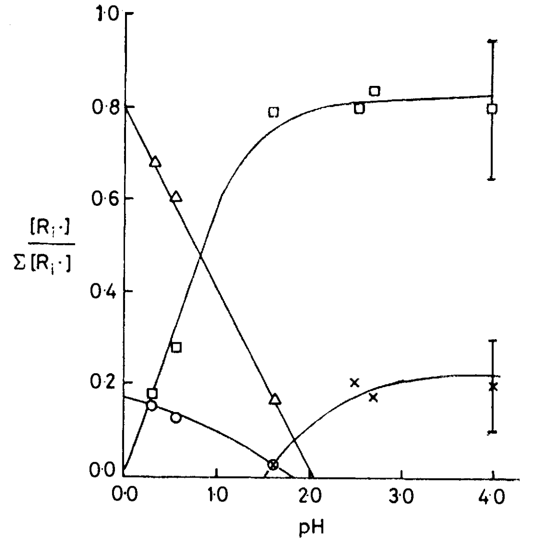
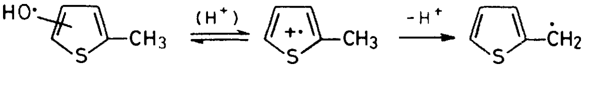


FIGURE 2 Relative proportions of radicals observed ([Rᵢ·]/Σ(Rᵢ·]) during the reaction of ·OH with 2-methylthiophen in the pH range 0—4: □, (10); △, (13); ×, (11); ○, (14)

Reaction with ·OH at pH > 7, when, by analogy with radical (1), radicals (10) and (11) are susceptible to ring-opening, yielded a complex spectrum which could not be analysed.

Reaction with $NH_3^{+\cdot}$ at low pH led to the detection of a complex spectrum which resembled to some extent that detected during the corresponding reaction with thiophen [which gave signals from (8) and (9)]. Details for the major radical detected, the 5-adduct (15), are given in the Table; an unambiguous analysis of the other lines present was not possible.

(ii) *Mechanistic implications.* In the reaction of 2-methylthiophen with ·OH, the distribution of isomeric hydroxy-adducts at pH > 4 evidently reflects the regioselectivity of ·OH attack. This appears to be largely governed by the extra stability afforded to (10) and (11), compared with the 3- and 4-adducts; the dominance of (10) over (11) may reflect both the extra stability conferred on the former by the possibility of hyperconjugative delocalization of spin density by the α-methyl substituent and the greater steric hindrance involved in the formation of the latter. The disappearance of (10)—(12) as the pH was lowered is analogous to the behaviour of (5); it is interpreted in terms of the acid-catalysed conversion of these into an intermediate radical-cation (16) which undergoes rapid deprotonation to give the thenyl radical (13) [reaction (11)].



(16) (13) (11)

The finding that 2-methylthiophen reacts with $Cl_2^{-\cdot}$, again presumably *via* electron-transfer, to give both (13) and the hydroxy-adduct (10) indicates that deprotonation of (16) is accompanied by hydration. Since both radicals were observed at pH *ca.* 2.0, higher than that at which acid-catalysed loss of hydroxide from adducts (10) and (11) in the reaction with ·OH becomes significant, it is inferred that the hydration reaction leading to (10) and (11) at that pH is irreversible, and therefore that the ratio of [(13)] : [(10)] of *ca.* 2 : 1 reflects the kinetic control of deprotonation *versus* hydration [to yield (10) and (11)] of the radical-cation. This result also establishes that (10) is the radical formed preferentially by attack of water on the radical-cation.

The relative ease with which (10)—(12) formed in reaction with ·OH undergo acid-catalysed loss of OH^- as the pH is lowered depends on two factors, namely the respective ground-state and transition-state energies. Since differences between the latter quantities are expected to be small (as a common intermediate is formed), the former should be the dominating influence, implying that the order of disappearance reflects the thermodynamic stabilities of the three species. Thus, in accord with expectations based upon radical structures, (12) disappeared at a significantly higher pH than (10) or (11).

Our observation that (10) and (11) undergo acid-catalysed reactions implies that (1), formed in the oxidation of thiophen with ·OH, also undergoes loss of OH^-, but at significantly lower rate, for a given pH, than (5) (see earlier). If this assertion is correct, then it follows that (1) is the thermodynamically preferred product of hydration of the thiophen radical-cation.

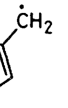
(c) *Reactions of* 3-*Methylthiophen.*—The reaction of ·OH with 3-methylthiophen (0.003 mol dm^{-3}) in the pH range 4—7 resulted in the detection of signals ascribable to the ·OH adducts (17)—(19); signals from (17) and (18) predominated {with [(17)] : [(18)] *ca* 1.2 : 1}, with (19) present in much lower concentration (the tentative assignment is based on the spectrum width and *g*-value). As the pH was lowered, the signal from (19) disappeared, and the concentration of (18) increased at the expense of that of (17); signals from S_1 appeared below pH 1.0. At pH 0.5, signals from (17) were not detected, although overlapping resonances and low signal-to-noise ratios would have rendered them undetectable at intensities *ca.* one-quarter of those from (18). In addition, at pH $<$ *ca.* 0.5, weak background signals from the thenoxyl radical

(20) were detected. The spectrum obtained during the reaction with ·OH at pH > *ca.* 7.0, when radicals (17) and (18) apparently undergo ring-opening, proved too complex for analysis.

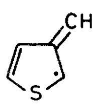
Reactions with $Cl_2^{-\cdot}$ were again carried out in the pH range 0—*ca.* 2, when both (18) and (20) were detected, the former being dominant. A significant increase in [(20)] was observed when the pH was lowered from *ca.* 1.5 to 1.0. With $NH_3^{+\cdot}$, overlapping signals from the appropriate adducts were detected (see earlier) but a full analysis proved impossible.

Our results imply that, assuming that their destruction rates are about the same, the two allylic adducts (17) and (18) are formed at approximately the same rates. However, under conditions of low pH where we believe that the relative proportions of (17) and (18) reflect their relative *thermodynamic* stabilities, the latter predomimates (possibly on account of the methyl substituent at the position bearing significant spin density); further, since (17) is detected in the reaction with ·OH at pH 1.5 but not in the corresponding reaction of $Cl_2^{-\cdot}$, which gives (18), it follows that, of the two, (18) is also the *kinetically* favoured product of hydration of the radical-cation.

These results also indicate that the radical-cation of 3-methylthiophen, in contrast to that of 2-methylthiophen, undergoes hydration in preference to deprotonation; no signals from the thenyl radical (21) were detected. We suggest that this reflects the relative stabilities of the deprotonated radicals (21) and (13), rather than significant differences in the properties of the intermediate radical-cations. Thus in (21) there is formal allyl-type delocalization of the unpaired electron only to C-2 [*cf.* structure (22)] whereas for the 2-substituted analogue (13) there is available greater (pentadienyl-type) conjugation from the radical centre to C-3 and -5.



(21)



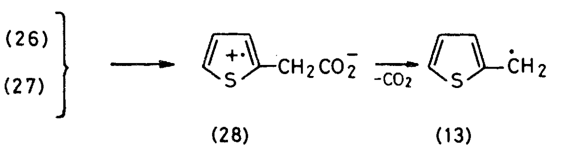
(22)

(d) *Reactions of 2-Thenylacetic Acid.*—Reaction of 2-thenylacetic acid (0.002 4 mol dm^{-3}) with ·OH at pH < 3 led to the detection of the 2-thenyl radical (13) and an adduct-radical assigned structure (23), in relative concentrations which varied markedly with pH. The radical (23) was the dominant species at pH 3.0 (with [(23)] : [(13)] *ca.* 2.2 : 1), but lowering the pH resulted in the enhancement of signals from (13) at the expense of those from (23) until at pH 0.5 only the former was detected. Oxidation with $Cl_2^{-\cdot}$ under similar conditions yielded only signals from (13), whereas reaction with $NH_3^{+\cdot}$ in this pH range led to the detection of a complex spectrum tentatively assigned to the adduct (24). No trace of (13) could be detected in this case [although the overlapping resonances would have precluded observation of a small (*ca.* 10%) contribution to the overall spectrum from this radical].

Oxidation of 2-thenylacetic acid by ·OH at pH values in excess of 4 (when the substrate, with pK_a 3.89,[18] is largely in its basic form) resulted in the detection of four species (though they did not all appear together at all pH values). One of these was the decarboxylated radical (13); the others are assigned the structures (25)—(27) [of these, the detailed analysis for the first two (see Table) leads to an unambiguous assignment, but the (incomplete) assignment to the third, which is made mainly on the basis of *g*-value and overall spectrum width, is tentative]. The parameters for (25) closely resemble those for the protonated analogue (23); as the pH was lowered below 4 the parameters for the radical detected moved monotonically from those of (25) to those of (23), consistent with there being rapid proton-exchange (so that an average of splittings for acid- and base-forms is detected) with pK_a *ca.* 3.75.

The relative proportions of the four species again varied considerably with pH. At pH 7.0 (25) was dominant, comprising *ca.* 75% of the mixture; (26) and (27) were detected in approximately equal proportions, with (13) undetectable at this pH. Lowering the pH to 5 resulted in the disappearance of (27) and the appearance of (13). Further lowering of the pH to 3.5 resulted in a further increase in the concentration of (13), at the expense of (26), so that at 3.5 the latter was not detected. The spectra obtained above pH 7 were complex and could not be completely analysed. However, certain trends were noted; thus the concentrations of (26) and (27) remained unaffected with increasing pH, whereas signals from (25) disappeared completely (presumably *via* base-catalysed ring opening; see earlier). Again, attempts to utilize $S_2O_8^{2-}$ at pH values >3 failed.

These results suggest that the kinetically controlled attack of ·OH on the anion from 2-thenylacetic acid favours the allylic adduct (25). Our failure to detect a 2-hydroxy-adduct (*cf.* the reaction with 2-methylthiophen) presumably reflects the retarding effect of steric hindrance in the transition state leading to its formation. The disappearance of the minor products (27) and (26) as the pH is lowered [presumably *via* acid-catalysed reactions to yield the intermediate radical-cation (28)] we interpret in terms of their lower stabilities compared with that of (25). Once formed, the radical-cation may in principle rehydrate, but our results suggest that, instead, decarboxylation [reaction (12)] occurs exclusively; this process is analogous to those proposed for the acid-catalysed decomposition of hydroxy-adducts of, for example, phenylacetic acid [13] and $S(CH_2CO_2H)_2$.[19]



(12)

We cannot unambiguously determine the regioselectivity of attack of ·OH on 2-thenylacetic acid itself, since at pH values less than 3.5 (which would be required to protonate the anion) the acid forms of (26) and (27) would be expected to yield (13) *via* an acid-catalysed process analogous to reaction (12). However, the presence of the saturated carbon atom between the carboxy-group and the ring should render differences in regioselectivity due to ionization small and we therefore believe that adducts corresponding to both (26) and (27) are initially formed, prior to rapid loss of hydroxide and fragmentation. Radical (25) also undergoes acid-catalysed loss of hydroxide, but in the lower pH range 1—2, so that the formation of (13) from (25), presumably *via* the protonated analogue of (28), can be detected in this case.

The detection of only (13) during the reaction with $Cl_2^{\cdot}$ is consistent with the occurrence of electron-transfer to give a radical-cation which undergoes decarboxylation [*cf.* reaction (12)]; we can exclude rehydration to give (25) as a competing reaction of the radical-cation since this radical would be detectable above pH *ca.* 1.5 (*cf.* the results of the reaction with ·OH).

The two other points are worthy of note. First, the detection of only (24) in the reaction with $NH_3^{+\cdot}$ confirms the preference of $NH_3^{+\cdot}$ for addition to, rather than electron abstraction from, thiophens, as well as the poor leaving-group ability of NH_3 compared with H_2O. Secondly, we failed to detect thenoxyl radicals in oxidations of 2-thenylacetic acid with either $Cl_2^{-\cdot}$ or ·OH, even in experiments in which Fe^{III} was added as an oxidant.

(e) *Reactions of Thiophen-2-carboxylic Acid and Its Anion.*—The state of protonation of thiophen-2-carboxylic acid (pK_a 3.52 [20]) would be expected to affect the selectivity of ·OH attack more than that of 2-thenylacetic acid. Likewise, a knowledge of the pK_a values of the various possible radical-adducts will be important in the interpretation of their behaviour as the pH is changed. Initial experiments were therefore carried out at extremes of pH to allow characterisation of the appropriate adducts; parameters for these [radicals (29)—(36)] are included in the Table.

Inspection of splittings for corresponding protonated and unprotonated radicals reveals that changes in parameters upon ionization are only significant for those pairs of radicals in which the unpaired electron is delocalized onto the carboxy-group. In all these cases, the change-over in parameters, as reflected in a broadening of the spectral lines, and a movement in their position, occurred in the pH range 2.5—4.0, which indicates that the pK_a values of the carboxy-conjugated adducts are *ca.* 3.25. One further point of structural interest is that the small doublet of 0.03 mT in (31) is not from the (exchangeable) β-OH group, since it was not ' averaged out ' at high acidities; we therefore assign it to the proton at C-5 [an additional broadening of the lines from (31) in the pH range 1.3—2.0 probably stems from exchange of the hydroxy proton].

In reactions with ·OH between pH 5 and 8 (when there was no evidence for ring-opening reactions) (33)—(36) were all detected, with relative concentrations *ca.* 2 : 2 : 1 : 1, respectively. As the pH was lowered to *ca.* 3.0, signals due to (36) (or its protonated counterpart) were removed and, as discussed above, signals from other radicals broadened somewhat. Further lowering of the pH to *ca.* 2.0 resulted in the complete replacement of signals from (33)—(35) by those of the protonated analogues (29)—(31), respectively. Below pH 1.5, the signal from the 5-adduct (29) increased in intensity at the expense of that from (30) and an additional, unidentified radical [with a(1 H) 2.09, a (1 H) 0.93, a (1 H) 0.235 mT, g 2.004 7] became detectable. At pH < 0 (H_0 *ca.* -0.5) only traces of (30) were detectable and a slight decrease in [(31)] was observed; traces of a signal attributable to the thenoxyl radical (32) were also detected under these conditions.

Reaction with $Cl_2^{-\cdot}$ at pH 1.9 resulted in the detection of (29), (30), and (32), in relative proportions *ca.* 4.5 : 1 : 0.5. The spectrum of (30) was again removed as the pH was lowered, though that from the thenoxyl species (32) increased in intensity with increasing acidity until pH 1.0, when the ratio [(29)] : [(32)] was *ca* 2.5 : 1. The signal from the latter also increased, at the expense of that from (29), when the reaction was carried out in the presence of Fe^{III}.

Finally, when oxidations were carried out with $SO_4^{-\cdot}$ at pH > 5.0, signals could only be detected from (33). The signal-to-noise ratio was poor, and other species present at concentrations *ca.* 20% of [(33)] would not have been detected.

The distribution of isomeric hydroxy-adducts in the reaction with ·OH in the pH range 5—8 is again interpreted in terms of the regioselectivity of ·OH addition to the carboxylate anion. Of the four adducts, the radical (36), which lacks both allylic stabilisation and delocalisation of the unpaired electron into the carboxy-group, evidently undergoes acid-catalysed loss of hydroxide most readily (although we cannot rule out the possibility that a change in the selectivity of ·OH attack with increasing extent of protonation of the parent compound contributes to the reduction in its concentration as the pH is lowered).* The disappearance of (30) at lower pH presumably reflects its rearrangement [again, like (36), presumably *via* acid-catalysed loss of hydroxide ion to give a radical-cation]; the radicals which remain, (29) and (31), are those which possess stabilisation energy derived from conjugation between the unpaired electron and the carboxy-group. The dominance of (29) at very low pH suggests that this is the thermodynamically favoured isomer (as would be expected since it possesses both allyl- and carboxy-delocalization), but it was not possible to determine whether or not this also undergoes an acid-catalysed reaction.

The reaction with $Cl_2^{-\cdot}$ demonstrates that (29) is also the kinetically preferred product of hydration of the intermediate radical-cation since, as inferred from the results with ·OH, the radicals (29)—(31) do not undergo

---

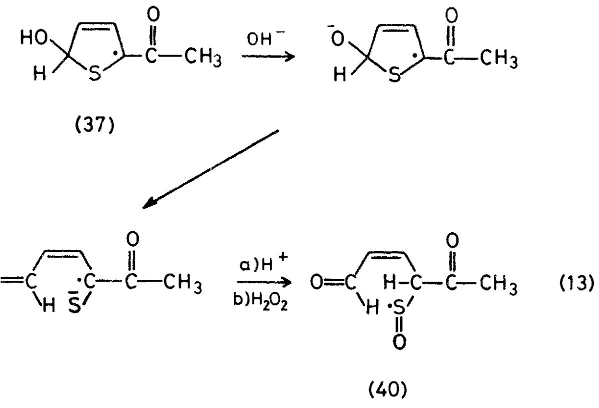
* The regioselectivity of attack of ·OH on the parent acid cannot be unambiguously determined, since it seems likely that the protonated form of (36) undergoes ready fragmentation; however, the dominance of (29) and (30) at pH *ca.* 2 probably reflects the kinetic preference of ·OH addition.

acid-catalysed conversion at a detectable rate above pH 1.5. This conclusion is supported by the results of the oxidation with $SO_4^{-\cdot}$ which yields (33), formed presumably by hydration of the intermediate radical-cation (though care must be exercised in the interpretation of experiments utilizing $SO_4^{-\cdot}$ since the distribution of radicals observed is likely to be affected by selective oxidation by $S_2O_8^{2-}$, reactions which probably also account for the low signal-to-noise ratio observed in these experiments).

Our detection of the thenoxyl species (32) at low pH with $Cl_2^{-\cdot}$ and with ·OH is in accord with our expectations based on results with other thiophen derivatives (see earlier).

(f) *Reactions of 2-Acetylthiophen.*—The reaction of acetylthiophen with ·OH in the pH range 0—2 led to the detection of a complex spectrum in which signals attributed to (37) and (38) could be discerned (the complexity results, at least in part, from other weak signals and possibly also from the occurrence of geometrical isomers of the former radical, *cf.* ref. 17). The former radical was dominant, the more so at the lower end of the pH range. When the pH was raised to *ca.* 2.0 a third, weaker signal, identified as the 4-adduct (39), also became detectable; its concentration relative to that of the other radicals remained unchanged up to pH 7.0. Although by analogy with the behaviour of thiophen-2-carboxylic acid, the formation of the 3-adduct would have been expected, no signals unambiguously assignable to this species were observed.

At pH > 7.0, signals from (37) and (38) were lost, and a signal from a fourth radical [with a(1 H) 0.475 and a(3 H) 0.088 mT, g 2.011 3] appeared. This is believed to be a sulphinyl radical (*cf.* the oxidation of thiophen itself at high pH), derived by molecular oxidation (with H_2O_2) of an intermediate radical formed by ring-opening of either (37) or (38); the formation of, for example, (40), from (37) [reaction (13)], would be consistent with our observations, though other structural and mechanistic possibilities exist and further speculation on the subsequent reactions of ring-opened radicals is unjustified.



(13)

Oxidation of 2-acetylthiophen by $Cl_2^{-\cdot}$ in the pH range 0—2 yielded only the radical (37) in detectable concentrations; weak (unanalysable) background signals were also present. No radicals were detected during the reaction between $SO_4^{-\cdot}$ and this substrate.

Our observations concerning the reactions of 2-acetylthiophen with $Cl_2^{-\cdot}$ and with ·OH at low pH are analogous to those described for other thiophen derivatives (see *e.g.* the Scheme). Thus direct addition of ·OH at pH > 2.5 gives the adducts (37)—(39), the first of these being kinetically preferred; as the pH is lowered, (39) undergoes acid-catalysed elimination of OH^- to give an intermediate radical-cation (obtained directly in the $Cl_2^{-\cdot}$ reaction) and thence, *via* rehydration, (37) and (38). Radical (38) is the next to undergo elimination as the pH is lowered further; the dominance of (37) at the lowest pH values studied reflects its thermodynamic stability compared with its isomers. It is also the kinetically-preferred product of hydration of the radical-cation, as judged by the results for $Cl_2^{-\cdot}$.

We also note that, as judged by the pH value at which the 4-adduct can still be detected as the solution is acidified (*ca.* 2.0), the radical-cation is formed much less readily than that from, *e.g.* the 4-hydroxy adduct of thiophen itself (for which the required pH is *ca.* 3.5). This presumably reflects the destabilising effect of the acetyl group on the radical-cation.

(g) *Conclusion.*—The complex series of observations concerning the reactions of ·OH, $NH_3^{+\cdot}$, and $Cl_2^{-\cdot}$ with thiophen and some derivatives as a function of pH can be rationalized as follows.

(i) Attack by ·OH proceeds *via* direct addition, with a general preference for reaction at the α-(2- or 5-) positions (this selectivity may reflect the extra allylic stability in the transition states leading to these, or the electrophilic nature of ·OH, or both), with the unsubstituted position itself preferred (presumably on account either of the steric hindrance at the substituted carbon or the stability afforded the radical by delocalisation of the unpaired electron by the substituents or both). These kinetic preferences may be obtained from studies at *ca.* pH 4—7, where neither base- nor acid-catalysed transformations are significant.

(ii) When the pH is lowered, the ratios of concentrations of hydroxy-adducts change (the pH at which this is noticed depends upon the substituent present), consistent with the occurrence of acid-catalysed dehydration of individual isomers followed by rehydration of the resulting radical-cations [see (iii)] and, in some cases, the appearance of signals from different types of radicals [see (iv)].

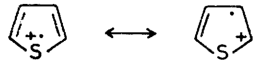
(iii) Loss of hydroxide occurs for a given substrate most readily from the 3- and 4-adducts rather than the 2- and 5-adducts (presumably reflecting the relative instability of the former pair) and, for a range of substrates, least readily from those with $-M$ substituents (which presumably destabilize the resulting radical-cation).

(iv) The radical-cation from 2-methylthiophen undergoes ready deprotonation, to give the appropriate thenyl radical, which is also obtained from the 2-thenylacetic acid radical-cation *via* deprotonation and decarboxylation.

(v) The appropriate radical-cations also result from direct electron-abstraction from the parent substrates by $Cl_2^{-\cdot}$ (though not in the reaction of $NH_3^{+\cdot}$ which leads simply to ammoniumyl adducts which show no tendency to undergo acid-catalysed reactions).

(vi) The ratio of hydroxy-adducts detected at the lowest pH values reached in the reactions with both ·OH and $Cl_2^{-\cdot}$ reflects the relative thermodynamic stabilities of the hydroxy-adducts (*i.e.* under these conditions rapid equilibrium is achieved); as expected, the 5-adduct is favoured for 2-substituted thiophens.

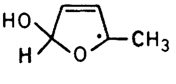
(vii) The reaction of $Cl_2^{-\cdot}$ with substrates at pH values above those at which equilibrium is established [see (vi)] yields relative concentrations of hydroxy-adducts which are governed by the *kinetic control of hydration* of the intermediate radical-cation; again, 2- and 5-attack is favoured. This may reflect a contribution to the transition state for formation of the α- rather than the β-adduct(s) of the extra (radical) delocalisation available for the former adducts; it is also possible that a contributing feature is the possession in the radical-cation itself of significant positive charge at the 2- and 5-positions [*cf.* structure (41) which, at least on the basis of e.s.r. results[21] for $CH_2{=}C(OMe)_2^{+\cdot}$ (which show that the unpaired electron is largely associated with the unsubstituted carbon) would be expected to make a significant contribution to the resonance hybrid].



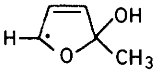
(41)

Our finding that thiophen radical-cations undergo preferential attack by water at the 2- and 5-positions and that the radical-cation from 2-methylthiophen also undergoes deprotonation is entirely consistent with the result of the electrochemical oxidation of 2,5-dimethylthiophen,[22] where products from both types of reaction have been obtained.

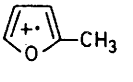
Lastly, it is of interest to compare the reactions of thiophen with those of furan under similar conditions. The reactions of a variety of furan derivatives with ·OH in the pH range *ca.* 0.3—10 have been previously described;[10] they are consistent with direct ·OH addition and, at high pH, ring-opening of the resulting adducts. They will not be further discussed. One further result of particular relevance is that reaction of ·OH (or $Cl_2^{-\cdot}$) with 2-methylfuran produces only the hydroxy-adducts (42) and (43), even at low pH when acid-catalysed reactions involving the radical-cation (44) are expected. We conclude that, in contrast to the reaction of the 2-methylthiophen radical-cation (16), which readily undergoes deprotonation, the radical-cation from 2-methylfuran is preferentially hydrated [*cf.* also product studies of the electrochemical oxidation of 2,5-dimethylfuran, for which no deprotonation occurred[22]].



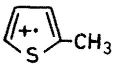
(42)



(43)



(44)



(16)

This notable difference, which is in accord with expectations based on some simple MO calculations,[22] may also be interpreted in terms of the greater stability of (44) compared with (16) [on account of the greater $+M$ effect of oxygen compared with that of sulphur (compare, for example, the $E_{\frac{1}{2}}$ values of furan and thiophen which are 1.70 and 1.91, respectively[23])], as well as the extra stability afforded to the thenyl radical (12), from (16), compared with the oxygen-substituted counterpart, by the spin-delocalising effect of the sulphur.[24]

EXPERIMENTAL

E.s.r. experiments were carried out with Varian E-104 and E4 spectrometers both equipped with 100 kHz modulation and an X-band klystron. Hyperfine splittings were measured directly from the spectrometer field-scan, which had previously been calibrated with reference to Fremy's salt [a(N) 1.309 1 mT[25]]; g-factors were measured by comparison with the signal from ·CHMeOH (generated from the reaction of ·OH with ethanol), which has g 2.003 3 (itself measured relative to the g factor for Fremy's salt, 2.005 5[26]). Assignments were usually checked by simulation of spectra on a DEC-KL10 computer at the University of York using a program which incorporates Lorentzian line-shape and second-order effects. Relative concentrations of radicals were determined from measurements of peak heights (where the appropriate line-widths were the same) or by comparison with simulated spectra (numerical double integration was not possible in most cases because of overlap of spectral lines). pH Measurements (to within ±0.05 units) were made continuously with a Pye PW9410 digital pH meter, coupled to a Russell pH Ltd. electrode inserted into the effluent stream.

All experiments employed an aqueous sample cell with a three-way mixing chamber (with a mixing time 80 ms); the flow was maintained by a Watson–Marlowe peristaltic pump. Typically, for reactions with ·OH, stream (i) contained 0.007 mol dm^{-3} titanium(III) [added as 12.5% (w/v) titanium(III) chloride solution (Fisons technical grade) or 15% (w/v) titanium(III) sulphate solution (Fisons technical grade)], stream (ii) contained *ca.* 0.035 mol dm^{-3} hydrogen peroxide [added as 100 volume hydrogen peroxide (B.D.H. Ltd.)], and stream (iii) contained the substrate at the required concentration. Concentrated sulphuric acid was usually added to stream (i) only to bring the pH (on mixing) to the required value. For experiments at pH > 2.5, edta (3 g dm^{-3}) was added to stream (i) and the pH was adjusted as required with either concentrated sulphuric acid or ammonia (d 0.880). For reactions with $SO_4^{-\cdot}$ and $NH_3^{+\cdot}$ stream (ii) contained instead 0.01—0.05 mol dm^{-3} potassium persulphate and 0.6 mol dm^{-3} hydroxylamine hydrochloride respectively. For experiments with $Cl_2^{-\cdot}$, sodium chloride was added to either stream (i) or to both streams (i) and (ii) to yield a concentration (after mixing) of a least 1 mol dm^{-3}. The concentration of substrate in stream (iii) was generally 0.000 5—0.05 mol dm^{-3}. In experiments where potassium hexacyanoferrate(III) was utilised this was usually added in the required concentration to stream (ii). All solutions were purged with nitrogen prior to flowing.

All materials were commercial samples which were used without further purification.

We thank B.P. Co. Ltd. for a studentship (for P. S. W.) and Dr A. J. Burn for helpful discussions.

[0/1098 *Received, 11th July, 1980*]

REFERENCES

[1] Part 58, B. C. Gilbert, R. O. C. Norman, and P. S. Williams, *J.C.S. Perkin II*, 1980, 647.

[2] See, *e.g.* E. J. Fendler and J. H. Fendler, *Progr. Phys. Org. Chem.*, 1970, **7**, 229; A. J. Swallow, *Progr. Reaction Kinetics*, 1978, **9**, 195.

[3] P. Neta, *Adv. Phys. Org. Chem.*, 1976, **12**, 224.

[4] J. Lilie, *Z. Naturforsch.*, 1971, **26b**, 197.

[5] B. B. Saunders, P. C. Kaufman, and M. S. Matheson, *J. Phys. Chem.*, 1978, **82**, 142.

[6] M. Bonifacic, H. Mockel, D. Bahnemann, and K.-D. Asmus, *J.C.S. Perkin II*, 1975, 675.

[7] B. C. Gilbert and P. R. Marriott, *J.C.S. Perkin II*, 1979, 1425.

[8] See, *e.g.* R. O. C. Norman, P. M. Storey, and P. R. West, *J. Chem. Soc.* (*B*), 1970, 1087.

[9] T. J. Stone and W. A. Waters, *Proc. Chem. Soc.*, 1962, 253.

[10] R. H. Schuler, G. P. Laroff, and R. W. Fessenden, *J. Phys. Chem.*, 1973, **77**, 456.

[11] R. O. C. Norman and R. J. Pritchett, *J. Chem. Soc.* (*B*), 1967, 378.

[12] B. C. Gilbert, C. M. Kirk, R. O. C. Norman, and H. A. H. Laue, *J.C.S. Perkin II*, 1977, 497.

[13] R. O. C. Norman and R. J. Pritchett, *J. Chem. Soc.* (*B*), 1967, 926.

[14] K. Bhatia and R. H. Schuler, *J. Phys. Chem.*, 1974, **78**, 2335.

[15] B. C. Gilbert, H. A. H. Laue, R. O. C. Norman, and R. C. Sealy, *J.C.S. Perkin II*, 1975, 892.

[16] B. C. Gilbert and P. R. Marriott, *J.C.S. Perkin II*, 1980, 191.

[17] A. Hudson and J. W. E. Lewis, *Tetrahedron*, 1970, **26**, 4413.

[18] E. Imoto and R. Motoyama, *Bull. Naniwa. Univ. 2A*, 1954, 127 (*Chem. Abs.*, 1955, **49**, 9614e).

[19] B. C. Gilbert, J. P. Larkin, and R. O. C. Norman, *J.C.S. Perkin II*, 1973, 272.

[20] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

[21] G. Behrens, E. Bothe, J. Eibenberger, G. Koltzenburg, and D. Schulte-Frohlinde, *Angew. Chem. Internat. Edn.*, 1978, **17**, 604

[22] K. Yoshida, T. Saeki, and T. Fueno, *J. Org. Chem.*, 1971, **36**, 3673.

[23] L. Eberson and K. Nyberg, *J. Amer. Chem. Soc.*, 1966, **88**, 1686.

[24] P. M. Carton, B. C. Gilbert, H. A. H. Laue, R. O. C. Norman, and R. C. Sealy, *J.C.S. Perkin II*, 1975, 1245.

[25] R. J. Faber and G. K. Fraenkel, *J. Chem. Phys.*, 1967, **47**, 2462.

[26] J. Q. Adams, S. W. Nicksic, and J. R. Thomas, *J. Chem. Phys.*, 1966, **45**, 654.