

Oxidation of 3-Hydroxythiophenes [Thiophen-3(2H)-ones]: an EPR Study of Monomeric and Dimeric Intermediates

Hamish McNab,^{*a} Gordon A. Hunter^a and John C. Walton^{*b}

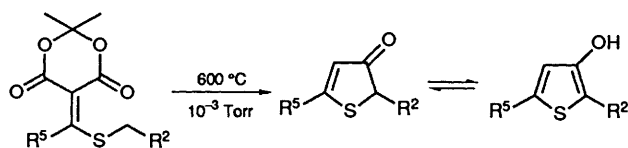
^a Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK

^b Department of Chemistry, University of St. Andrews, St. Andrews, Fife KY16 9ST, UK

Hydrogen abstraction from thiophen-3(2H)-ones gives 3-oxothiophen-2-yl radicals which have been observed by EPR spectroscopy at temperatures below ambient. The structures, enthalpies of formation, and spin densities of these species have been investigated by semiempirical SCF MO methods. The radicals readily couple to give dimers (except for 2-substituted 3-hydroxythiophenes) are susceptible to a second hydrogen abstraction step to give extensively delocalized dimeric radicals; EPR spectroscopy showed the 5,5'-disubstituted dimeric radicals to be significantly persistent even at higher temperatures. A mechanism for the oxidation of thiophen-3(2H)-ones by air and one-electron oxidants is proposed and justified.

2,2-Unsubstituted 3-hydroxythiophenes [thiophen-3(2H)-ones] are readily oxidized by air or one-electron oxidizing agents to give dehydromers.¹ 2-Substituted derivatives also give dehydromers, but these may be replaced by, or accompanied by, products coupled through oxygen.² We recently proposed a mechanism to account for the formation of dehydromers and other products in the oxidation of the structurally related 3-hydroxypyroles.³ The key steps were dimerization of intermediate monomeric 3-oxopyrrol-2-yl radicals and loss of a hydrogen atom from the dimer to give dimeric radicals. The monomeric radicals could not be identified with certainty by EPR spectroscopy, but the dimeric species were observed and spectroscopically characterized in several cases.

It seemed likely to us that analogous intermediates would be important in the autoxidation, and other homolytic reactions, of 3-hydroxythiophenes (1) and 3-hydroxyfurans. Accordingly, we have made a study of radical generation from 3-hydroxythiophene, and a range of substituted 3-hydroxythiophenes, which were prepared according to a recently discovered route⁴ involving flash vacuum pyrolysis of Meldrum's acid derivatives (Scheme 1).



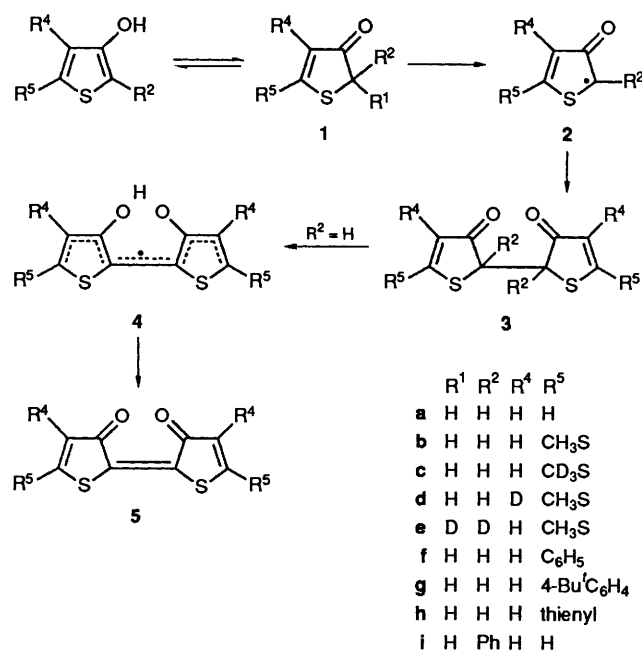
Scheme 1

In this paper we report the EPR spectroscopic observation and characterization of both monomeric and dimeric radical intermediates derived from homolytic reactions of 1. We also discuss the mechanism of 3-hydroxythiophene autoxidation in the light of the EPR and other evidence.

Results and Discussion

The 3-hydroxythiophene (1), together with di-*tert*-butyl peroxide, in a hydrocarbon solvent, usually *tert*-butylbenzene, was photolysed in the cavity of an EPR spectrometer. The photochemically produced *tert*-butoxyl radicals then abstract hydrogen from the substrate. The spectrum obtained from the parent 3-hydroxythiophene (1a) in the temperature range 220–260 K, which consisted of four doublets, is shown in Fig. 1. This spectrum suggested that the species under observation was the 3-oxothiophen-2-yl radical 2a (Scheme 2).

On closing the lamp shutter the spectrum decayed within the



Scheme 2

response time of the spectrometer, indicating that the radical lifetime was $\leq 10^{-3}$ s. At higher temperatures, and after longer photolysis times, the spectrum of Fig. 1(a) was replaced by a much stronger signal [Fig. 1(b)] (*vide infra*). Similar spectra, which we attribute to the monomer radicals 2b and 2i, were observed on hydrogen abstraction from the substituted 3-hydroxythiophenes 1b and 1i, respectively.

The measured EPR hyperfine splittings (hfs), are given in Table 1. As expected, the greatest spin density is associated with H² and, in the case of the 2-phenyl derivative 2i, the large hfs from H² is replaced by substantial hfs from the hydrogens of the phenyl ring. The hfs of H⁴ and H⁵ showed small changes with temperature, but $a(\text{H}^2)$ was constant to within experimental error. Two substituted 3-oxothiophen-2-yl radicals, having hfs of comparable magnitudes, have been reported by Nootens *et al.*⁵

In view of our success in observing the monomer 3-oxothiophen-2-yl radicals 2, further attempts were made to observe the analogous 3-oxopyrrol-2-yl radicals 6³ by hydrogen abstraction from the corresponding 3-hydroxypyroles. For *N-tert*-butyl-3-hydroxypyrole, weak, ill-resolved signals from

Table 1 EPR hyperfine splittings for 3-oxothiophen-2-yl radicals **2**^a

Radical	T/K	H ²	H ⁴	H ⁵	Other
2a	250	1.26	0.16	0.13	—
2a	INDO ^b	[−1.12]	[−0.22]	[0.19]	[—] ^b
2b	230	1.42	0.07	—	0.07 (3 H)
2i	240	—	0.10	0.10	0.48 (H _m) 0.38 (2 H _α) 0.2 (2 H _β)

^a In mT. ^b Computed hfs, see the text.

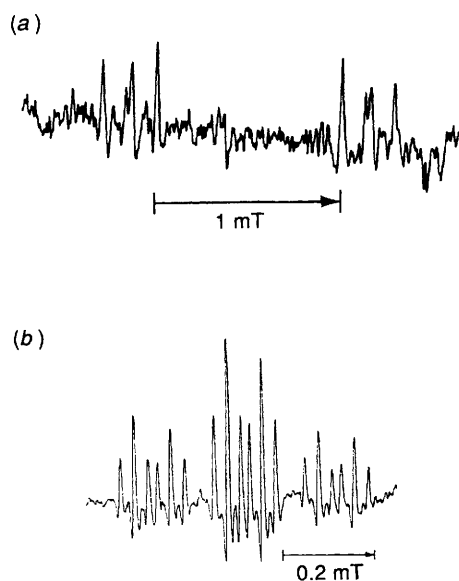
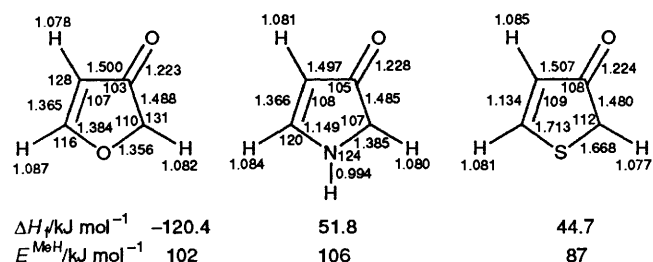


Fig. 1 9.3 GHz EPR spectra (second-derivative presentation) of radicals derived from **1a** in *tert*-butylbenzene solution: (a) 3-Oxothiophen-2-yl radical **2a** at 250 K; (b) dimer radical **4a** at 320 K

transient species were observed, which were probably due to **6b**, but the spectral quality was too poor for analysis. The EPR spectrum of one member of the 3-oxofuran-2-yl series **7b** has been reported.⁵ We were only able to observe a broad weak signal (ΔH_{pp} ca. 1.0 mT) for radical **7c** on hydrogen abstraction from the corresponding furanone.

The structures and enthalpies of formation, ΔH_f° , of the archetypal radicals **2a**, **6a** and **7a** and their precursors **1a** *etc.*, were calculated by the semiempirical MNDO SCF method.⁶ The fully optimized structures are shown in Fig. 2. The

**Fig. 2**

furanone and thiophenone radicals were calculated to be planar, but the pyrrolone radical was slightly pyramidal at nitrogen, the HNCC dihedral angle being 170°. The structures and enthalpies of formation show a rather consistent picture for these radicals. The bonds α to the radical centre at C(2) are all significantly shorter than in the precursor molecules and the bonds β to the radical centre are all significantly longer; this pattern of changes is normal for free radicals. The C(4)=C(5)

double bonds were virtually unchanged, but the C(3)=O double bonds increased by ca. 0.005 Å from the values in the precursor molecules. The calculated coefficients of the SOMOs indicated that although the unpaired electron was mainly associated with C(2) there was significant delocalization onto the ring heteroatoms and into the C(3)=O double bonds; as would be expected for capto-dative (C-D) radicals of this type. The MNDO structure of the 3-oxothiophen-2-yl radical **2a** (Fig. 2) was used in a Zerner INDO-type calculation.⁷ The calculated hfs were gratifyingly close to the experimental values (Table 1) and this supports our identification of these transient species as 3-oxothiophen-2-yl radicals **2**. The INDO calculated $a(\text{H}^4)$ was larger than $a(\text{H}^5)$ and we have assigned the larger experimental hfs to H⁴ on this basis. Obviously the hfs of these two hydrogens are too similar for this assignment to be regarded as fully established.

The stabilization energies of radicals **2a**, **6a** and **7a** (designated R^{*}) relative to the methyl radical, E^{MeH} , were calculated from the computed enthalpies of formation of the radicals and their precursors using eqn. (1).⁸ The computed

$$E^{\text{MeH}} = \Delta H_f^\circ(\text{CH}_3^\cdot) - \Delta H_f^\circ(\text{CH}_4) - \Delta H_f^\circ(\text{R}^*) + \Delta H_f^\circ(\text{RH}) \quad (1)$$

E^{MeH} values (Fig. 2) are fairly large, and indicate that these C-D radicals have substantial thermodynamic stabilization, comparable to that of the pentadienyl radical (75–120 kJ mol^{−1}).⁹ It is not surprising therefore that all three types of radical were easily and selectively generated from the 3-hydroxy heterocycles in solution in preference to other modes of radical formation from these precursors. Although the 3-oxopyrrolyl radicals **6**, and the 3-oxofuranyl radicals **7**, were more difficult to observe by EPR spectroscopy, this is most likely due to their rapid further reactions and not to any difficulty with their formation.

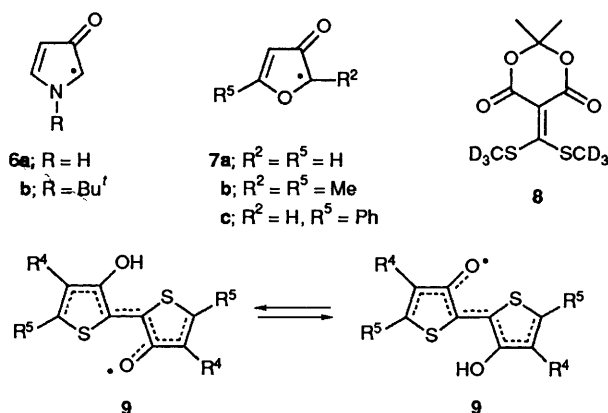
When the solution of **1a** was warmed to above ca. 300 K, or on prolonged photolysis, the spectrum of the monomer radical was replaced by a new one [Fig. 1(b)] showing six triplets. This pattern is that expected for the dimer radical **4a**. Similar intense spectra were obtained from a variety of substituted thiophenones, often after short induction periods, and the hfs are given in Table 2.

The assignment of the hfs to specific hydrogens was achieved by using ²H-labelled precursors **1c**, **d** and **e**. The compounds labelled in the 2-position (**1e**) and 4-position (**1d**) were obtained from the corresponding unlabelled material **1b**, by *in situ* exchange using deuterium oxide, and by acid-catalysed deuteration respectively (see the Experimental section). The 5-[²H₃]methylthio derivative **1c** was made by pyrolysis of **8** to give a perdeuterated version of **1b**, followed by protium exchange at the 2- and 4-positions in trifluoroacetic acid. The radical, **4c**, obtained from the 5-CD₃S-substituted precursor, did not show the large triplet splitting, which could therefore be assigned to H^{5,5'}. The radical derived from **2d**, with the deuterium label at C(4), did not show either of the triplet hfs; thus confirming that the smaller of these corresponds to H^{4,4'}. Finally, the singlet hfs was missing from the spectrum obtained

Table 2 EPR hyperfine splittings for dimer radicals **4**^a

Radical	T/K	H(OH)	H ^{4,4'}	H ^{5,5'}	Other
4a	330	0.155	0.060	0.390	—
4b	320	0.133	0.066	—	0.07 (6 H)
4c	340	0.135	0.070	—	—
4d	320	0.133	—	—	0.07 (6 H)
4e	320	—	0.066	—	0.07 (6 H)
4f	340	0.133	0.077	—	0.077 (4 H _o) 0.04 (4 H _p) 0.031 (2 H _m)
4g	340	0.133	0.077	—	0.077 (4 H _o) 0.031 (2 H _m)
4h	340	0.136	0.108	—	0.112 (4 H) 0.028 (2 H)

^a Hfs in mT, checked by computer simulations where appropriate.



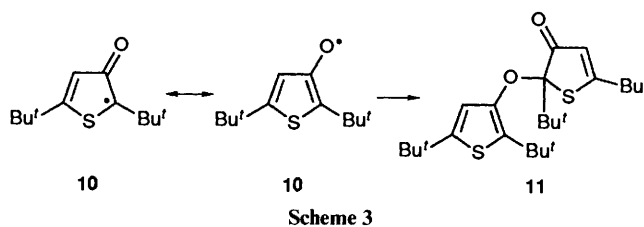
from the 2,2-dideuterio-material (**1e**), which confirmed the assignment of this splitting to the chelated hydrogen atom of the dimer radical. Comparison of these hfs with those of the analogous dimer radicals obtained from pyrrol-3(2H)-ones,³ showed many similarities, the main differences being (i) that radicals **4** have larger $a(\text{OH})$ values and (ii) slightly smaller hfs from the ring hydrogens. This implies a larger contribution to the ground state of **4** from resonance structures with the unpaired electron on oxygen. For both the thiophenone and pyrrolone dimer radicals the largest hfs were obtained for H^{5,5'}. This is easily justified in frontier orbital terms or by consideration of the resonance structures of the dimer radicals.³

Radical **4a** was very short-lived, but radicals **4b–e** had lifetimes of ca. 10 s at 300 K and radicals **4f–h** had lifetimes of many minutes even at 330 K. For the latter three radicals it was not possible to observe the monomer radical, probably because the spectrum is so rapidly swamped by the intense spectrum of the dimer radical. The persistence of these radicals can be attributed to steric shielding of the high electron density centres which inhibits reaction. No dimer radical was observed from the 2-phenyl derivative **1i**, of course, because the coupled product **3** (R² = Ph) has no hydrogen at the 2-position to be abstracted.

Two planar conformations can be envisaged for the dimer radicals, the *Z*-conformation **4** and the *E*-conformation **9**. In principle, these conformers could interconvert by rotation about the central partial double bond and, provided the barrier is low enough, this should lead to exchange broadening in the EPR spectra. We examined the spectra of radical **4b** in the temperature range 270–390 K, but no line broadening was discernible. Conformer **4** is probably the lowest-energy species because the symmetrical hydrogen bonding will confer additional stabilization. The internal rotation to give **9** most likely has too high a barrier to be detected in the accessible temperature range. We were not able to detect the EPR spectra of dimer radicals derived from **7c**.

Several attempts were made to isolate and characterize the

products from the oxidation of **1a** and **1b** with di-*tert*-butyl peroxide, but without success. After 14 h photolysis with a medium-pressure mercury lamp some substrate was still present and solid intractable polymeric material was formed. However, previous identifications of dehydromers from thiophenone oxidations,^{1,2} and the present EPR observations of both monomer and dimer radical intermediates, strongly suggest that the mechanism of oxidation follows that previously outlined for 3-hydroxypyrroles.³ By analogy, the primary radical reaction of thiophen-3(2H)-ones will be hydrogen abstraction from C(2) to give the radicals **2** (Scheme 2). C-D Radicals are known to dimerize particularly readily,¹⁰ and thus there are good precedents for the combination step. In the presence of an excess of oxidizing agent the dimer **3** will very easily undergo a second hydrogen abstraction because of the extensive resonance stabilization of the dimer radicals **4**. Interestingly, from the oxidation of 3-hydroxy-2,5-dimethylthiophene, where the second hydrogen abstraction cannot occur, the racemic and *meso* forms of **3** were isolated.² The EPR parameters of the monomer radicals **2**, and the SCF MO calculations, suggest that they have significant unpaired spin on oxygen. Thus resonance structures such as **10** (Scheme 3) will make a significant contribution to the ground electronic state.



Coupling *via* oxygen is therefore a viable possibility, and this was actually observed for the 2,5-di-*tert*-butyl derivative, for which **11** was isolated on exposure to air.² The bulky *tert*-butyl substituent impedes dimerization to **3** and consequently, the coupling reaction is diverted to **11**, which cannot undergo a further hydrogen abstraction, because the *tert*-butyl substituents occupy the relevant sites.

Experimental

Thiophen-3(2H)-ones and Furan-3(2H)-ones.—Compounds **1a, b** and **f–i** were obtained by flash vacuum pyrolysis of the appropriate 5-thiomethylene Meldrum's acid derivative, and have been previously reported.⁴ The furanone **7c** was made by the literature method¹¹ and had m.p. 84–85 °C (lit.,¹¹ 84–85 °C); $\delta_{\text{H}}(\text{CDCl}_3)$ 7.36–7.76 (5 H, m), 6.00 (1 H, s) and 4.60 (2 H, s); $\delta_{\text{C}}(\text{CDCl}_3)$ 201.98, 186.68, 132.57, 128.70, 128.56, 126.85, 101.29 and 75.16.

5-([²H₃]Methylthio)thiophen-3(2H)-one 1c.—5-([²H₃]methylthio)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione was pre-

pared in 50% yield from Meldrum's acid, carbon disulfide and [$^2\text{H}_3$]iodomethane in dimethyl sulfoxide containing triethylamine, as described by Huang and Chen.¹² Flash vacuum pyrolysis at 600 °C⁴ gave [$^2\text{H}_6$]thiomethylthiophen-3(2H)-one as a solid, m/z 152 (M^+ , 5%), 151 (8), 150 (8), 76 (91), 74 (22), 58 (47) and 46 (100). This perdeuteriated compound (30 mg) was dissolved in trifluoroacetic acid (0.5 cm³), and the solution was monitored by ^1H NMR spectroscopy until back-exchange at the 2- and 4-positions was complete. The solution was then neutralized with dilute aqueous sodium hydrogen carbonate solution, and the required 5-([$^2\text{H}_3$]thiomethyl) derivative was obtained by extraction with dichloromethane [$\delta_{\text{H}}(\text{CDCl}_3)$ 5.9 (1 H, s) and 3.6 (2 H, s)].

[4- ^2H]-5-Methylthiophene-3(2H)-one **1d**.—A solution of the unlabelled thiophenone^{4,13} (30 mg) in [O - ^2H]trifluoroacetic acid was monitored (as above) until exchange at the 2- and 4-positions was complete. Neutralization with dilute aqueous sodium hydrogen carbonate and work-up as described for **1c** above caused complete back-exchange at the 2-position to give the [4- ^2H]isotopomer (^2H incorporation ca. 80%); $\delta_{\text{H}}(\text{CDCl}_3)$ 2.5 (3 H, s) and 3.7 (2 H, s).

[2- $^2\text{H}_2$]-5-Methylthiophene-3(2H)-one **1e**.—This species was generated *in situ* from the unlabelled material^{4,13} by shaking the *tert*-butylbenzene solution prior to irradiation, with D_2O .

EPR Spectra.—These were recorded at 9.3 GHz on a Bruker ER 200D spectrometer with 100 kHz modulation. Samples of the 3-hydroxythiophene (ca. 10 mg) and di-*tert*-butyl peroxide (50 mm³) were dissolved in *tert*-butylbenzene (0.5 cm³) and degassed by being purged with nitrogen for ca. 10 min. They were sealed in 4 mm o.d. Spectrosil tubes and irradiated in the cavity of the spectrometer with light from a 500 W super-pressure mercury lamp. Spectra were simulated using a modified version of Heinzer's program.¹⁴

Acknowledgements

We thank the University of Edinburgh for the award of the Colin and Ethel Gordon Scholarship (to G. A. H.).

References

- 1 A. I. Kosak, R. J. F. Palchak, W. A. Steele and C. M. Selwitz, *J. Am. Chem. Soc.*, 1954, **76**, 4450.
- 2 A.-B. Hornfeldt and P.-O. Sundberg, *Acta Chem. Scand.*, 1972, **26**, 31.
- 3 H. McNab, L. C. Monahan and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1988, 759.
- 4 G. A. Hunter and H. McNab, *J. Chem. Soc., Chem. Commun.*, 1990, 375; A. J. Blake, G. A. Hunter and H. McNab, *J. Chem. Soc., Chem. Commun.*, 1990, 734.
- 5 C. Nootens, R. Merenyi, Z. Janousek and H. G. Viehe, *Bull. Soc. Chim. Belg.*, 1988, **97**, 1045.
- 6 J. J. P. Stewart, *QCPE*, Program No. 455, University of Indiana, Indiana, 1983; M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899, 4901.
- 7 M. C. Zerner, G. H. Loew, R. F. Kirchner and U. T. Muller-Westerhoff, *J. Am. Chem. Soc.*, 1980, **102**, 589.
- 8 M. J. S. Dewar, M. A. Fox and D. J. Nelson, *J. Organomet. Chem.*, 1980, **185**, 157; A. G. Davies, D. Griller, K. U. Ingold, D. A. Lindsay and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1981, 633.
- 9 J. C. Walton, *Rev. Chem. Intermed.*, 1984, **5**, 249.
- 10 H. G. Viehe, Z. Janousek, R. Merenyi and L. Stella, *Acc. Chem. Res.*, 1985, **18**, 148, and references therein.
- 11 J.-F. Robert and J. J. Panouse, *C. R. Acad. Sci., Ser. 2*, 1982, **294**, 249.
- 12 X. Huang and B.-C. Chen, *Synthesis*, 1986, 967.
- 13 A. Ben Cheikh, H. Dhimane, J. C. Pommelet and J. Chucho, *Tetrahedron Lett.*, 1988, **29**, 5919.
- 14 J. Heinzer, *QCPE*, Program No. 209, University of Indiana, Indiana, 1972.

Paper 2/00630H

Received 5th February 1992

Accepted 18th February 1992