Electrophilic Substitution on the Thiophen Ring. Part 5.† The Effect of Methyl Groups on the Kinetics of Hydrogen Exchange in Acidic Media

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The effect of methyl groups on the rate of protodetritiation of 2- and 3-tritiothiophen in perchloric acid has been examined and activation parameters for the reactions have been calculated. The activating effect of a second methyl is non-additive. Reaction at the 3-position is less susceptible to substituent effects than that at the 2-position. With 2-methyl-, 2,4-dimethyl-, and 2,5-dimethyl-thiophen, as well as ring hydrogen exchange, there is slower exchange on certain methyl groups.

HYDROGEN exchange on thiophen compounds has been investigated by a number of workers and it is agreed that the 2- is more reactive than the 3-position.[1] These studies have confirmed a number of theoretical investigations.[2] The variation of the rate of exchange at both the 2- and 3-positions with acidity is consistent with an A–S_E2 mechanism.[3] The effect of a number of substituents at the 5-position on the rate of protodetritiation at the 2-position was investigated by Butler and Eaborn [4] but little else is known about the transmission of substituent effects in thiophen for hydrogen exchange. In this report we describe a study of the effects of methyl groups on hydrogen exchange at both the 2- and 3-positions. The results may be compared with the transmission of substituent effects for electrophilic substitution on pyrrole.

RESULTS AND DISCUSSION

Data obtained for exchange at the 2-position in 0.085M-perchloric acid are given in Table 1. Extrapolation of the results of Butler and Hendry [3] to 0.085M-acid gives a value of $k_{obs.}$ for protodetritiation of 2-tritiothiophen of 1.15×10^{-7} s^{-1} at 25°. This figure, com-

† Part 4, A. R. Butler and J. B. Hendry, *J. Chem. Soc.* (*B*), 1971, 102.

[1] K. Halvarson and L. Melander, *Arkiv. Kemi*, 1955, **9**, 29; B. Östman and S. Olsson, *ibid.*, 1960, **15**, 275; R. Taylor, *J. Chem. Soc.* (*B*), 1968, 1397; A. I. Shatenshtein, A. G. Kammrad, I. O. Shapiro, Y. I. Ramneva, and E. N. Zvyagintseva, *Doklady. Akad. Nauk, S.S.S.R.*, 1966, **168**, 364; K. Schwetlick, K. Unverferth, and R. Meyer, *Z. Chem.*, 1967, **7**, 58.

[2] K. Klasinc and K. Humski, *Z. Naturforsch.*, 1970, **25b**, 324; M. Janda, J. Šrogl, I. Stibor, P. Trška, and P. Vopatrná, *Coll. Czech. Chem. Comm.*, 1974, **39**, 3522.

[3] A. R. Butler and J. B. Hendry, *J. Chem. Soc.* (*B*), 1970, 852.

[4] A. R. Butler and C. Eaborn, *J. Chem. Soc.* (*B*), 1968, 370.

bined with the results in Table 1, gives the activating effect of a methyl group at positions 3—5 on the rate of exchange at the 2-position (Table 2). The extrapolation

TABLE 1

Protodetritiation of substituted 2-tritiothiophen in 0.085M aqueous perchloric acid

Substituent(s)	Temperature (°C)	$10^5 k_{obs.}/s^{-1}$
(a) 5-Me	27.0	2.23
	35.2	4.62
	45.3	9.36
	55.2	18.4
(b) 4,5-Me_2	27.3	2.63
	35.2	5.10
	45.0	10.8
	55.1	23.3
(c) 3,5-Me_2	27.3	65.3
	35.2	108
	45.0	212
	55.1	444

TABLE 2

Activating effect of a methyl group towards hydrogen exchange on the thiophen ring at 27°

Compounds compared	Position of protodetritiation	Position of methyl group	Activating effect
Thiophen and (a)	2	5	194
(a) and (b)	2	4	1.2
(a) and (c)	2	3	29

of the results of Butler and Hendry [3] is a long one and so the value in Table 2 for the 5-methyl group is subject to uncertainty. There is also a small error due to the difference in temperature of the two determinations. The value obtained agrees well with that (*ca.* 200) determined by Butler and Eaborn [4] for protodetritiation in trifluoroacetic acid.

Compounds (b) and (c) contain two methyl groups and the effect of the second methyl group on the rate of protodetritiation is more difficult to understand. The effect of a methyl group at the 'diagonal' position in (b) is small, but this is not unexpected as there is no resonance effect in the Wheland intermediate for a methyl group at that position. The effect of an extra methyl group at the 3-position in (c) on exchange at the 2-position is surprisingly small. It would be expected that its effect would be similar to that of a 5-methyl group. However, our results indicate that, with both methyl groups present in the molecule, their effects on protodetritiation are not additive.

Shatenshtein *et al.*[5] report that 3-methyl-2-tritiothiophen is protodetritiated in trifluoroacetic acid 340 times faster than 2-tritiothiophen. This may be compared with the activating effect of a 5-methyl group of 194 reported by Butler and Eaborn.[4] This is the evidence for the similar activation by 3- and 5-methyl groups. There is no evidence from previous work that, in thiophen compounds, the effect of two methyl groups is additive. Ansell and Taylor [6] found that activating effects were not additive in the protodetritiation of tritiated xylenes. Katritzky *et al.*[7] have reported similar behaviour with a number of five-membered aromatic heterocycles. However, these effects are smaller than that observed in the present work. A more direct comparison can be made with work of Shatenshtein *et al.*[8] on the protodedeuteriation of deuteriated phenylthiophens. For exchange at the 2-position both 5- and 3-phenyl groups activate the reaction to comparable extents. On the other hand, with 4,5-diphenylthiophen exchange is actually slightly slower than with 5-phenylthiophen, a result which is in agreement with our result for 4,5-dimethylthiophen. However, these workers found that in 3,5-diphenylthiophen the effect of the phenyl groups is additive. Our results for 3,5-dimethylthiophen are not in agreement with this observation and there is no obvious explanation for this. The value for the 5-methyl group, owing to the long extrapolation, is subject to considerable uncertainty and the difference between our results and those of Shatenshtein *et al.*[8] may be less than the figures in Table 2 suggest. On the other hand, it may be greater.

From the results recorded in Table 1 activation parameters for protodetritiation at the 2-position have been calculated (Table 3). Changes in rate of reaction are

TABLE 3

Activation parameters for the protodetritiation of methylthiophens at 40°

Compound	$[HClO_4]$/M	Position of proto-detritiation	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal $mol^{-1} K^{-1}$
(a)	0.085	2	14.0 (±0.3)	−33 (±2)
(b)	0.085	2	14.6 (±0.3)	−31 (±2)
(c)	0.085	2	13.6 (±0.5)	−28 (±2)
(d) *	3.98	3	16.4 (±0.5)	−21 (±2)
(e) *	3.98	3	16.0 (±0.4)	−22 (±2)
(f) *	3.98	3	15.5 (±0.5)	−23 (±2)
(g) *	3.98	3 (4)	13.4 (±0.4)	−31 (±2)

* See Table 4.

due to changes in the enthalpy of activation and, as far as can be judged from the limited data, the entropy of activation remains constant at *ca.* 31 cal mol^{-1} K^{-1}. This value is very different from that measured by Butler and Hendry [3] for protodetritiation of thiophen in concentrated sulphuric acid (14.6 cal mol^{-1} K^{-1}). This is probably due to differences in hydration of the proton in the two media.

Hydrogen exchange at the 3-position of thiophen is much slower than at the 2-position and results for the protodetritiation of substituted 3-tritiothiophen in

[5] E. N. Zyvagintseva, T. A. Yakushina, and A. I. Shatenshtein, *Zhur. obshchei Khim.*, 1968, **38**, 1993.

[6] H. V. Ansell and R. Taylor, *J. Chem. Soc.* (*B*), 1968, 526.

[7] S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1675; S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, *ibid.*, 1974, 399.

[8] E. N. Zvyagintseva, V. E. Udre, M. G. Voronkov, and A. I. Shatenshtein, *J. Gen. Chem.* (*U.S.S.R.*), 1971, **41**, 2314.

3.95M-perchloric acid are given in Table 4. Exchange with unsubstituted 3-tritiothiophen in this acid was found to be too slow to determine and so we have no measure of the effect of a single methyl group at the 4-position. However, comparison of the values of $k_{obs.}$

TABLE 4

Protodetritiation of substituted 3-tritiothiophen in 3.95M aqueous perchloric acid

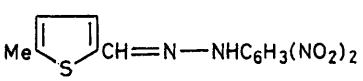
Substituent(s)	Temperature (°C)	$10^3 k_{obs.}/s^{-1}$
(d) 4-Me	27.0	0.166
	35.2	0.311
	45.3	1.02
	55.2	1.86
(e) 4,5-Me_2	27.0	0.280
	35.2	0.643
	45.5	1.31
	55.0	2.94
(f) 2,4-Me_2	27.0	0.282
	35.2	0.491
	45.3	1.29
	55.2	2.24
(g) 2,5-Me_2	27.0	0.154
	35.2	0.286
	45.5	0.566
	55.0	0.966

for (e) and (f) with those for (d) shows that introduction of a second methyl group, wherever it is located, has very little effect on the rate. For a 5-methyl group this is reasonable as it is diagonally situated with respect to the site of reaction. A much larger effect is anticipated for a methyl group at the 2-position, as in (f), as here the substituent is *ortho* to the site of reaction. Even if the effect of a second methyl group is not additive, the activating effect of that group is still surprisingly small. It is much less than the effect of a 3-methyl group on exchange at the 2-position. There is an explanation for this. One distinctive feature of the thiophen ring is the large difference in reactivities of the 2- and 3-positions, much larger than for pyrrole.[9] If introduction of a methyl substituent lowers the activation energy of reaction by a similar amount, then a methyl group will affect reaction at the 2- much more than at the 3-position. The substituent effect for compound (f) is consistent with this analysis.

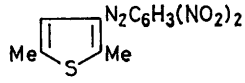
Activation parameters for protodetritiation at the 3-position have been calculated from the data in Table 4 and are given in Table 3. The difference in the reactivity of the 2- and 3-positions is caused by changes in both the enthalpy and entropy of activation. The situation is complicated by the fact that the parameters were determined at different acidities and, as has already been noted, this may cause a change in the entropy of activation. The activation parameters for protodetritiation of 2,5-dimethyl-3-tritiothiophen are significantly different from those for exchange at the 3-position with compounds (d)—(f). At present we can offer no explanation for this. The more negative value of $\Delta S^{\ddagger}$ for (g) could indicate a change of mechanism, but it is difficult to see what this change could be.

One reason for this study was to compare the transmission of substituent effects in thiophen and pyrrole rings with respect to electrophilic substitution. The latter situation has been described by an examination [10] of the reaction between pyrrole and 4-dimethylaminobenzaldehyde in acid solution. In this reaction a methyl group at the 5-position has a smaller effect on reaction at the 2-position than in protodetritiation of 2-tritiothiophen. However, with pyrrole a 3-methyl group has a similar effect to a 5-methyl group but, as we have seen, this is not true for the protodetritiation of 2-tritiothiophen. The explanation for this cannot be steric as the thiophen is free of steric interaction between *ortho*-positions [11] and hydrogen exchange is less subject to steric inhibition than other reactions. The constancy of the entropies of activation for protodetritiation, even in the presence of an *o*-methyl group, indicates that there is no change of mechanism which could explain the effect. This does not apply, of course, to (g). The explanation may lie in the role of the sulphur atom in determining the reactivity of the thiophen molecule.

In a study of the reaction between various polymethylthiophens and 2,4-dinitrophenyldiazonium ions Tedder *et al.*[12] found that, as well as the expected ring attack there may be reaction with a methyl group. For example 2,5-dimethylthiophen reacts to give (I) as well

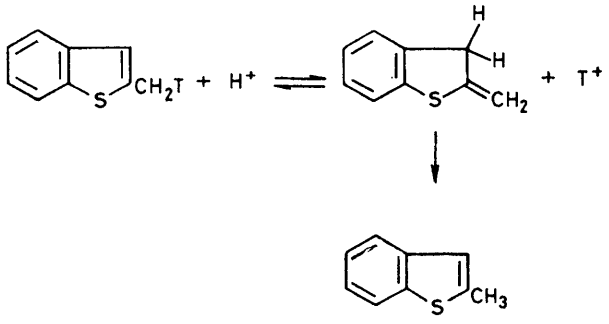


(I)



(II)

as (II). Reaction with a methyl group does not occur with less activated benzenediazonium ions. Eaborn and Wright [13] reported that for 2-methylbenzothiophen in acid solution, there is exchange of both the ring and methyl group hydrogens. They propose the mechanism shown in the Scheme for methyl group hydrogen



SCHEME

exchange. A similar mechanism explains the formation of (I). There is, however, one problem associated with

[9] A. Grossauer, 'Die Chemie der Pyrrole,' Springer-Verlag, Berlin, 1974, p. 105.

[10] R. S. Alexander and A. R. Butler, *J.C.S. Perkin II*, 1976, 696.

[11] D. Spinelli, R. Noto, G. Consiglio, and A. Storace, *J.C.S. Perkin II*, 1976, 1805.

[12] S. T. Gore, R. K. Mackie, and J. M. Tedder, *J.C.S. Perkin I*, 1976, 1639.

[13] C. Eaborn and G. J. Wright, *J. Chem. Soc.* (*B*), 1971, 2262.

this mechanism. Eaborn and Wright [13] reported that, for 2-methylbenzothiophen, ring exchange is at least 2 000 times faster than exchange on the methyl group, whereas for the reaction of 2,5-dimethylthiophen with 2,4-dinitrobenzenediazonium ions, reaction occurs equally readily on the ring and with the methyl group. It was decided, therefore, to examine the rate of hydrogen exchange on the methyl group and the ring of 2,5-dimethylthiophen itself. For exchange of the methyl group hydrogens $k_{obs.}$ in 3.98M-perchloric acid was found to be 1.29×10^{-5} s^{-1}, only 45 times slower than exchange of a ring proton in the same acid. While this result does not explain fully why (I) forms as readily as (II), the very large difference in the reactivity of ring and methyl protons, observed with 2-methylbenzothiophen, does not apply to 2,5-dimethylthiophen.

Tedder *et al.*[12] also measured hydrogen exchange on the methyl groups of a number of methylthiophens by examining changes in the ^1H n.m.r. spectra with time when the compounds were dissolved in deuteriotrifluoroacetic acid. They observed immediate exchange of all the ring protons followed by much slower exchange of the protons in certain methyl groups. Gore [14] reports that exchange of the methyl protons of 2,5- and 2,4-dimethylthiophen is very slow and incomplete after many hours. This result appears to confirm the large difference in reactivity of ring and methyl group protons reported by Eaborn and Wright.[13]

We repeated the work of Gore [14] and have interpreted the results in the light of our studies of the kinetics of hydrogen exchange. With 2,4-dimethylthiophen in deuteriotrifluoroacetic acid exchange of the ring protons was complete before the first n.m.r. spectrum could be recorded. Over the next 6 h there was gradual exchange of the protons of the 2-methyl group, but reaction ceased when about half the protons had exchanged. There was no exchange on the 4-methyl group. Our previous results indicate that the high acidity of neat trifluoroacetic acid [15] should lead to very rapid exchange of the ring protons in both the 3- and 5-positions. However, we would have expected exchange of the methyl group protons to be complete within the period of the experiment. The fact that this does not occur can be explained in terms of the experimental conditions. In order to obtain n.m.r. spectra the initial concentration of 2,4-dimethylthiophen, which contains five exchangeable hydrogens, was *ca.* 0.9M. As exchange proceeded the deuteriotrifluoroacetic acid contained increasing amounts of protium and the final situation was an equilibrium one. The apparent decrease in the rate of deuteriodeprotonation of the 2-methyl group was due to the kinetics of the approach to equilibrium.

Similar results were obtained with 2-methylthiophen. About 50% deuteriodeprotonation of the methyl group occurred during 6 h. With 3-methylthiophen no exchange on the methyl group occurred and 2,3-dimethylthiophen decomposed during the course of the reaction.

EXPERIMENTAL

Materials.—Thiophens tritiated at all the ring positions were prepared by stirring the appropriate compounds (0.5 g) overnight with a mixture of 60% H_2SO_4 (1 ml) and tritiated water (1 ml; 50 mCi ml^{-1}). The resultant mixture was neutralised with an excess of NaOH and extracted with ether (50 ml). After washing with water (2 × 25 ml) the solution was dried ($MgSO_4$) and the solvent removed by evaporation. Tritiodeprotonation of the methyl groups of 2,5-dimethylthiophen was effected in a similar manner by the use of tritiotrifluoroacetic acid. The tritiated thiophen was distilled before use.

2,3-Dimethylthiophen was prepared by a literature method.[16] Deuteriotrifluoroacetic acid was obtained by reaction of trifluoroacetic anhydride with deuterium oxide.

Kinetics.—The general method has been described previously.[3] Exchange at different positions on the thiophen ring occurs at very different rates and the reactions do not interfere with one another. For instance, in the acid used for exchange at the 3-position exchange at the 2-position is so rapid that it is complete within 5 min. On the other hand, in 0.085M-perchloric acid essentially no protodetritiation occurs at the 3-position. The rate constants were calculated by the method of Swinbourne and Kezdy.[17]

N.m.r. Studies.—A solution of the thiophen in deuteriotrifluoroacetic acid (0.9M), with an equal amount of dichloromethane as a standard, was prepared and spectra were recorded at timed intervals. When the thiophen had a methyl group which did not undergo exchange its signal remained constant with reference to that for dichloromethane and showed that the thiophen was stable in trifluoroacetic acid.

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[16] J. Lamy, D. Lavit, and Ng. Ph. Buu-Hoï, *J. Chem. Soc.*, 1958, 4202.
[17] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371; F. J. Kezdy, J. Jaz, and A. Bruylants, *Bull. Soc. chim. belges*, 1958, **67**, 687.