Electrophilic Aromatic Substitution. Part 33.[1] Partial Rate Factors for Protiodetritiation of Benzo[*b*]thiophen; the Resonance-dependent Reactivity of the Ring Positions

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Rate coefficients for detriation of benzo[*b*]thiophen, specifically labelled with tritium at each position, have been measured in anhydrous trifluoroacetic acid, and, for [2-^{3}H]benzo[*b*]thiophen, in a range of trifluoroacetic acid–acetic acid mixtures, all at 70°. The dependence of rate upon acidity is consistent with the effect of hydrogen bonding between sulphur and trifluoroacetic acid, as found previously for other sulphur-containing heterocycles. Partial rate factors, corrected for the effect of hydrogen bonding are (positions in parentheses): 8.84×10^5 (2); 1.18×10^6 (3); 360 (4); 13 200 (5); 16 200 (6); and 26.2 (7); the corresponding σ^+ values are −0.68, −0.695, −0.29, −0.47, −0.48, and −0.16. The positional reactivity order is the same as found in pyrolysis of 1-arylethyl acetates, and solvolysis of 1-arylethyl chlorides, but the σ^+ values are more negative due to the greater demand for resonance stabilization of the transition states in hydrogen exchange. Comparison of the 2- : 3-isomer ratios in various substitutions leads to the unexpected conclusion that substitution at the 2-position is subject to steric effects, probably due to the proximity of the sulphur *d*-orbitals.

In this series of papers we have determined quantitatively the electrophilic reactivities of a range of sulphur-containing aromatic compounds,[1,2] molecules for which literature data are either sparse or non-existent. One feature which has emerged from this work is the anomalous reactivity *versus* acidity pattern, similar to but less marked than that found with oxygen-containing aromatic compounds such as anisole, and attributed to the same cause, *viz.* hydrogen bonding between sulphur (or oxygen) and trifluoroacetic acid. The effect of this bonding is that on going to less acidic media there is a smaller decrease in rate than found for aromatic compounds (*e.g.* alkylbenzenes) which are not hydrogen bonded. The magnitude of the variation of rate with acidity parallels the number of sulphur atoms in the molecule, thereby providing strong support for our view that hydrogen bonding is the cause of this variation. A further test of this hypothesis would be to see if benzo[*b*]thiophen would have the same rate *versus* acidity dependence as thiophen since both have one sulphur atom. An additional reason for studying this molecule is because there have been only two previous assessments of the electrophilic reactivities of all the ring positions,[3,4] and although these produced the same positional reactivity order, there were marked discrepancies in the σ^+ values of a given position. This we attributed to polarisability effects *i.e.* the ring positions are very susceptible to the demand for resonance stabilisation of the transition states for the particular reaction, and their reactivities are therefore inadequately described by a single sigma parameter. Data are also available (Table 2) for true electrophilic substitutions of the 2- and 3-positions, and these further indicated that a wide variation in sigma values is obtained. Values for these positions obtained previously in hydrogen exchange were significantly higher than those obtained in reactions producing a side-chain carbocation,[3] and it was therefore of interest to see if the values obtained in hydrogen exchange of the other (benzenoid) positions would similarly prove to be exalted relative to the side-chain reaction values. The hydrogen exchange data would be the first complete set obtained in electrophilic substitution of benzo[*b*]thiophen, providing in addition a basis for evaluating results for other sulphur-containing heterocycles as they become available.

Results and Discussion

The rate data are given in Table 1. For the 2-tritiated compound, rates were obtained in weaker acid media (mixtures of trifluoroacetic acid and acetic acid) in order to assess the effect of hydrogen bonding (see below) but this was not possible for the positions in the benzenoid ring because the rates

Table 1. Rate coefficients (10^7k/s^{-1}) and partial rate factors (f) for protiodetritiation of [X-^{3}H]benzo[*b*]thiophen and [2-^{3}H]thiophen

	Vol.% TFA in HOAc				
X	35	50	100	k(corr) [a]	f
2	9.1	72	19 900	84 000	88 400
3			26 600 [b]	112 000	118 000
4			8.1	34.2	360
5			29.7	1 250	1 320
6			365	1 540	16 200
7			0.59	2.49	26.2
[2-^{3}H]Thiophen	910	7 400	2.2×10^6	9.3×10^6	9.75×10^7
k(benzo[*b*]thiophen) / k(thiophen)	0.0090	0.0097	0.0100		

[a] See text. [b] Taken from ref. 20.

Table 2. σ^+ Values for various reactions of benzo[*b*]thiophen at position *X*

Reaction	$X = 2$	3	4	5	6	7	Ref.
Pyrolysis, 1-arylethyl acetates	−0.39	−0.54	−0.155	−0.29	−0.32	+0.10	3
Solvolysis, 1-arylethyl chlorides	−0.49	−0.56	−0.25	−0.34	−0.42	−0.11	4
Protiodetritiation	−0.68	−0.695	−0.29	−0.47	−0.48	−0.16	This work
Solvolysis, 1-arylethyl acetates	−0.43	−0.52					5
Protiodesilylation	−0.33	−0.34					6
Positive bromination	−0.39	−0.69					7
Acetylation	−0.49	−0.58					7
Molecular chlorination	−0.61	−0.77					7
Molecular bromination	−0.61	−0.77					7

would have been inconveniently slow. The main points which emerge from these data are as follows.

(1) *The Effect of Hydrogen Bonding.*—Hydrogen bonding in hydrogen exchange is identified by the variation in rate with composition of the medium consisting of trifluoroacetic acid with varying amounts of acetic acid.[8] If on going to media containing less trifluoroacetic acid the exchange rate decreases less than for an aromatic compound such as an alkylbenzene which is clearly not hydrogen bonded, then this points to a reduced rate (due to hydrogen bonding) in the more acidic medium. The variation in rate with acidity for [2-^{3}H]benzo[*b*]thiophen compared to that for [2-^{3}H]thiophen (previously shown to be hydrogen bonded [1]) is seen from the ratios at the bottom of Table 1. The acidity dependencies are very similar, so not only is benzo[*b*]thiophen hydrogen bonded, but the extent of his bonding is again proportional to the number of sulphur atoms, as was found for thienothiophens [1] and dithienothiophens.[2]

Rate data were not obtained in media weaker than 35 vol. % trifluoroacetic in acetic acid because the exchange rates would have been inconveniently slow. Previously we found that hydrogen bonding of thiophen is virtually absent in 15 vol. % trifluoroacetic acid in acetic acid,[2] and from the rate of exchange of thiophen and mesitylene in this medium it may be calculated that in pure trifluoroacetic acid the rate of exchange of thiophen is suppressed 4.22-fold by hydrogen bonding. Accordingly we have used this factor to correct the exchange rates for benzo[*b*]thiophen * to those which would apply in the absence of hydrogen bonding. These corrected values are given in Table 1 along with the derived partial rate factors from which the σ^+ values given in Table 2 are calculated.

(2) *The Positional Reactivities.*—The σ^+ values obtained in the hydrogen exchange and other reactions are given in Table 2, from which it can be seen that the positional reactivity order found in the previous two side-chain reactions, *viz.* $3 > 2 > 6 > 5 > 4 > 7$, is also found in hydrogen exchange. This would not necessarily be expected because the positional order could depend upon the nature of the transition state, and hence the polarisability of the molecule. Reactions with transition states nearer to the ground state should give correlations of rates with π-electron densities, whereas those with transition states nearer to products should give correlations of rates with localization energies. Previously we showed that the simple Hückel MO method (using recommended parameters for sulphur) gave π-electron densities which predicted precisely the reactivity order in pyrolysis of 1-arylethyl acetates (and also solvolysis of 1-arylethyl chlorides).[3] These therefore predict the order in hydrogen exchange which is rather surprising because data in this reaction are usually very well correlated with localization energies. This is true also for sulphur-containing heterocycles *e.g.*, thienothiophens,[1] dithienothiophens,[2] and dithienobenzenes [9] (again using the same parameters for sulphur). However for benzo[*b*]thiophen localization energies predict the order $2 > 3 > 4 > 7 > 6 > 5$ which is completely wrong for the positions in the benzenoid ring. The prediction in the thiophen ring is not so unsatisfactory since the 2- and 3-positions are very close in reactivity in hydrogen exchange, *i.e.* we are close to the point of ' crossing-over ' of the reactivities which is required as the transition state becomes more product-like in nature. {This ' crossing over ' is well established (and predicted) for benzo[*b*]furan [3] but has not been observed for benzo[*b*]thiophen.}

Table 3. Hückel MO calculations on benzo[*b*]thiophen with $\alpha_S = \alpha_C$, and $\beta_{CS} = 0.6\beta_{CC}$

Position	π-Electron density	$\Delta E/-\beta$
2	1.090	1.875
3	1.180	1.852
4	1.027	2.140
5	1.043	2.262
6	1.046	2.230
7	1.024	2.195

Given that the crossing over should occur, then it would be reasonable to expect that the 2-position would be more reactive than the 3-position in molecular chlorination and bromination since the ρ factors are greater than in hydrogen exchange.[10] It could be argued that the observed results arise from rearrangement of an initially formed 2-isomer to the 3-isomer, which we find can occur quite readily. However we do not consider this to be the primary cause of the anomaly because in acetylation (which has a ρ-factor almost identical to that in hydrogen exchange) not only is the 3-isomer again the major product, but under the same conditions, benzoylation (which is known to be less sterically hindered) gives almost twice as much 2-isomer.[7] We suggest therefore that electrophilic substitution of the 2-position of benzo[*b*]thiophen may be sterically hindered. This is perhaps rather unexpected since sites in five-membered rings are generally

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* We make the assumption that the factor applies equally to positions in the thiophen and benzene rings. This appears to be justified by our (unpublished) results for dithienobenzenes, compounds which give rate coefficients for the benzene rings accessible under a wider range of conditions than does benzo[*b*]thiophen.

less crowded. However we are persuaded to the steric argument by the fact that in protiodesilylation, a reaction with a transition state nearer to the ground state, we would expect a high 3- : 2-rate ratio. In fact the positional reactivities are almost equal and this would be very nicely explained by steric acceleration of 2-substitution, since this reaction is well known to be sterically accelerated in crowded situations.[11] These arguments are based on the Hückel predictions which support but are not central to our analysis. Even if these are disregarded we are still left with the problem that the variation of the 2- : 3-isomer ratios cannot be described solely in terms of electronic effects.

Lastly, the results in Table 2 confirm our previous observation that there is a marked dependence of the σ^+ values upon the reaction. We believe these variations to be due to the different demands for resonance stabilization of the transition states for the reactions, and as a consequence the ' Extended Selectivity Relationship '[12] is inapplicable to any of the positions.

Experimental

In the following preparations, benzo[*b*]thiophen was obtained with m.p. 29—31 °C and a small sample was purified for kinetic studies using t.l.c. (silica, 1 : 1 v/v hexane–chloroform as eluent).

[2-^{3}H]*Benzo*[b]*thiophen*.—n-Butyl-lithium (2.5 ml of a 1.6N solution in hexane) was dissolved in THF (10 ml) and added dropwise to a stirred solution of benzo[*b*]thiophen under nitrogen, the mixture being stirred during a further 1 h. Tritiated water (50 μl of 100 mC ml^{-1} specific activity) was added, the mixture stirred during a further 20 min and hydrolysis completed with excess of water.

[4- *and* 6-^{3}H]*Benzo*[b]*thiophen*.—m-*Bromothiophenol*. *m*-Bromoaniline (68 g, 0.5 mol) was diazotised in the usual way,[13] and converted *via* the literature method to *m*-bromothiophenol (45.3 g, 50%), b.p. 50—52 °C at 0.1 mmHg (lit.,[14] 119—121 °C at 20—22 mmHg).

m-*Bromophenyl* 2,2-*diethoxyethyl sulphide*. Reaction of *m*-bromothiophenol (43.5 g, 0.23 mol) with 2-bromo-1,1-diethoxyethane (45.3 g, 0.23 mol) according to the general literature method[15] gave *m*-bromophenyl 2,2-diethoxyethyl sulphide (87%), b.p. 115 °C at 0.85 mmHg, n_D^{20} 1.5492. G.l.c. analysis indicated this product to be >98% pure.

4- *and* 6-*Bromobenzo*[b]*thiophen*. *m*-Bromophenyl 2,2-diethoxyethyl sulphide (30 g, 0.11 mol) was cyclised with polyphosphoric acid according to the general literature method[16] to give a mixture of 4- and 6-bromobenzo[*b*]thiophens. Kinetic studies subsequently showed that 95% of this product must in fact be the 6-isomer. This however is not unexpected since the cyclisation involves alkylation, an electrophilic substitution known to be sterically hindered, so that substitution *ortho* to bromine is difficult.

Reaction of the mixture of bromo compounds with n-butyllithium followed by hydrolysis with tritiated water in the usual way gave [4- and 6-^{3}H]benzo[*b*]thiophen.

[5-^{3}H]*Benzo*[b]*thiophen*.—p-*Bromobenzenesulphonyl chloride*. This compound, m.p. 75—76 °C (lit.,[17] 75.4 °C), was prepared in 89% yield from bromobenzene according to the literature method.[18]

p-*Bromothiophenol*. *p*-Bromobenzenesulphonyl chloride (128 g, 0.5 ml) was reduced to *p*-bromothiophenol (78%), m.p. 74—75 °C (lit.,[14] 74—75 °C) according to the literature method.[14]

p-*Bromophenyl* 2,2-*diethoxyethyl sulphide*. Reaction of *p*-bromothiophenol (71 g, 0.38 mol) with 2-bromo-1,1-diethoxyethane (74.9 g, 0.38 mol) according to the literature method[15] gave *p*-bromophenyl 2,2-diethoxyethyl sulphide (82%), b.p. 86—88 °C at 0.4 mmHg.

5-*Bromobenzo*[b]*thiophen*. Cyclisation of *p*-bromophenyl 2,2-diethoxyethyl sulphide (50 g, 0.18 mol) with polyphosphoric acid according to the literature method[16] gave, after work up, 5-bromobenzo[*b*]thiophen, b.p. 50—52 °C at 0.5 mmHg, m.p. 47—48 °C (lit.,[15] 47.5 °C).

Reaction of 5-bromobenzo[*b*]thiophen with n-butyllithium followed by hydrolysis with tritiated water and normal work up gave [5-^{3}H]benzo[*b*]thiophen.

[7-^{3}H]*Benzo*[b]*thiophen*.—o-*Bromothiophenol*. This compound, b.p. 52 °C at 0.35 mmHg, was prepared in 45% yield from *o*-bromoaniline by the literature method.[13]

o-*Bromophenyl* 2,2-*diethoxyethyl sulphide*. Reaction of *o*-bromothiophenol with 2-bromo-1,1-diethoxyethane by the literature method[15] gave *o*-bromophenyl 2,2-diethoxyethyl sulphide (71%), b.p. 118—120 °C at 1.0 mmHg, n_D^{20} 1.5523 (lit.,[15] 130—131 °C at 7 mmHg). G.l.c. analysis indicated this compound to be >95% pure.

7-*Bromobenzo*[b]*thiophen*. Cyclisation of *o*-bromophenyl 2,2-diethoxyethyl sulphide as above gave 7-bromobenzo[*b*]thiophen (48%), b.p. 70—72 °C at 0.4 mmHg (lit.,[15] 108—109 °C at 10 mmHg).

Reaction of 7-bromobenzo[*b*]thiophen with n-butyllithium as above gave [7-^{3}H]benzo[*b*]thiophen.

Kinetic Measurements.—The general method has been described previously.[19] Rates were measured for each compound in anhydrous trifluoroacetic acid at 70°, and excellent first-order kinetics were obtained except with the mixture of 4- and 6-tritiated compounds which gave curved plots of log activity *versus* time, as expected. These were easily resolved into good first-order plots in the usual way, and from those it was possible to show that the position which had the slowest exchange rate was also present in relatively small amount. Steric considerations of the ring closure leading to the 4- and 6-isomers confirmed that the minor and least reactive component must be the 4-isomer.

The results are given in Table 1 along with those obtained previously for the 3-isomer.[20] Rate coefficients for the 2-isomer agreed within experimental error with those reported previously.[20] For this isomer rate coefficients were also measured in mixtures of AristaR acetic acid and trifluoroacetic acid, as given in Table 1.

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