The Quantitative Electrophilic Reactivity of Annulenes. Part 5.[1] Trithiadiazepine, its 6-Bromo- and 6-Nitro-derivatives, and Trithiatriazepine

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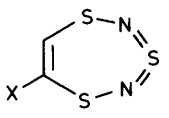
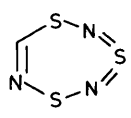
The quantitative electrophilic reactivities of the 10π-annulenes *viz.* 1,3λ⁴δ²,5,2,4-trithiadiazepine (**1**), 6-bromo-1,3λ⁴δ²,5,2,4-trithiadiazepine (**2**), 6-nitro-1,3λ⁴δ²,5,2,4-trithiadiazepine (**3**), and 1,3λ⁴δ²,5,2,4,6-trithiatriazepine (**4**) have been determined *via* acid-catalysed hydrogen exchange (protiodetritiation). Partial rate factors (for exchange in trifluoroacetic acid at 70 °C) are: 2.78×10^5 (**1**), 3.15×10^4 (**2**), *ca.* 0.038 (**3**), and *ca.* 0.006 (**4**), the corresponding σ^+-values being −0.62, −0.515, *ca.* 0.16, and *ca.* 0.25; the former two values are corrected for the effect of hydrogen bonding which reduces the reactivity of heteroaromatics in this medium. 1,3λ⁴δ²,5,2,4-trithiadiazepine is, thus, slightly more reactive than the 3-position of thiophene. Deactivation by the *ortho*-bromo substituent (ninefold) is much less than in benzene (37-fold) due to the higher order C–C bond in 1,3λ⁴δ²,5,2,4-trithiadiazepine which facilitates transmission of the conjugative electron-releasing (+*M*) effect of bromine; the small deactivation is comparable to that found across the 1,2-bond in naphthalene which is of similar bond order to that in 1,3λ⁴δ²,5,2,4-trithiadiazepine.

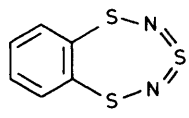
An intriguing new class of heteroaromatic compounds containing nitrogen and sulphur in seven-membered rings have been described recently by Rees *et al.*[1,2] These are 1,3λ⁴δ²,5,2,4-trithiadiazepine (**1**), the bromo- and nitro-derivatives (**2**, **3**), 1,3λ⁴δ²,5,2,4,6-trithiatriazepine (**4**) and benzo[*f*]-1,3λ⁴δ²,5,2,4-



(**1**) X = H
(**2**) X = Br
(**3**) X = NO_2



(**4**)



(**5**)

trithiadiazepine (**5**). Compounds (**1**), (**4**), and (**5**) have been shown to undergo normal electrophilic substitution.[1,2] We now report determination of the quantitative electrophilic reactivity of (**1**)–(**4**), *via* acid-catalysed hydrogen exchange (protiodetritiation).

Results and Discussion

Each of the compounds (**1**)–(**4**) was labelled by exchange with trifluoroacetic acid containing a little tritiated water of high specific activity. In compounds (**2**)–(**4**) only one site is available for exchange, whilst in (**1**) both sites are equivalent.

1,3λ⁴δ²,5,2,4-Trithiadiazepine (**1**) *and 6-Bromo-1,3λ⁴δ²,5,2,4-trithiadiazepine* (**2**).—For these compounds exchange rate measurements were carried out in trifluoroacetic acid (TFA) and TFA–acetic acid media, and both compounds gave excellent first-order kinetics (Table 1). Before the rate data could be analysed it was necessary to allow for the effect of hydrogen bonding which reduces the reactivity of ethers[4] (and probably of sulphides) towards detritiation, and has been shown to likewise reduce the reactivity of thiophene, benzo[*b*]thiophene, thienothiophenes, dithienothiophenes, and dithienobenzenes.[5] The effect of hydrogen bonding may be detected by carrying out exchange rate measurements in progressively weaker media,

Table 1. Detritiation of ArH in TFA–HOAc media at 70 °C.

	$k/10^{-7}$ s^{-1} in TFA:HOAc (v/v)		
Compound	100%	75%:25%	50%:50%
Mesitylene	674 500[a]		1 850
Durene	113 540[a]	11 600	
(**1**)	1 820	318	15.0
(**2**)	206	33.1	

[a] Taken from ref. 3.

and by comparing the decrease in rate with decreasing acidity with that for a compound (such as an alkylbenzene) which does not hydrogen bond. For compounds which hydrogen bond, the rate of fall-off with decreasing acidity will be less than for a compound which is not hydrogen bonded. By measuring the exchange rates for the alkylbenzene and the hydrogen-bonding aromatic compound in a medium in which hydrogen bonding is relatively insignificant, the true reactivity of the hydrogen-bonding aromatic compound under standard conditions (100% TFA) may be calculated. For the *S*-containing heteroaromatics noted above, the extent of hydrogen bonding was proportional to the number of sulphur atoms in the molecules and was effectively absent in TFA–HOAc (15:85 v/v).[5]

Nitrogen-containing heteroaromatics can be expected to be hydrogen bonded or even protonated in TFA. For example, gas-phase reactivity data indicate that hydrogen bonding in protic media reduces the reactivity of each position in pyridine by *ca.* 0.3 sigma units.[6] This corresponds to a rate reduction by *ca.* 250 times in hydrogen exchange, greater than that found for the *S*-containing compounds, the reactivities of the most affected dithienothiophenes being reduced by *ca.* 45 times in TFA. The relative positional reactivities in thiazole are also substantially altered by hydrogen bonding[7] but there are no data presently available for isothiazole, which would be the most pertinent to the molecules considered here.

The data in Table 1 show that compounds (**1**) and (**2**) are both hydrogen bonded, since the reduction in their rates of exchange are less with decreasing acidity than for either durene or mesitylene. This is more clearly seen from the data in Table 2

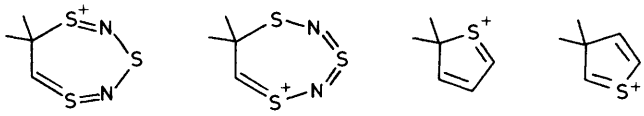
Table 2. Factors by which exchange rates in various TFA–HOAc mixtures (v/v) are reduced relative to exchange rates in TFA.

Compound	TFA:HOAc (v/v) 75:25	50:50	35:65	15:85
Mesitylene		400	5 230	196 000
Durene	9.78			
Thiophene		210	2 420	46 000
(**1**; X = Br)	6.22			
Thienothiophenes[a]	5.93	135	950	16 750
(**1**; X = H)	5.72	120	(850)	(13 500)
Anisole			720	9 000
Dithienothiophenes			550	

[a] Dithienobenzenes give very similar factors.

which show the factors by which the exchange rate coefficients are reduced in a given medium compared with exchange in TFA. These rate–acidity profiles show the susceptibility of (**1**) and (**2**) towards hydrogen bonding to be slightly greater than for thienothiophenes, but less than for dithienothiophenes which similarly have three sulphur atoms. It seems probable that the electron-withdrawing effect of the adjacent nitrogens reduces the susceptibility of the sulphurs to form hydrogen bonds. By the same token, one would expect the nitrogens to be strongly hydrogen bonded which, evidently, is not the case. Presumably, therefore, protonation rather than hydrogen bonding occurs at nitrogen, but we are observing only the exchange which takes place on the (hydrogen-bonded) free base. We may rule out the possibility that exchange is taking place on the hydrogen-bonded conjugate acid, because the combination of the high ρ-factor for hydrogen exchange in TFA and the relatively low exchange rates in this medium, imply that exchange on the conjugate acid would be too slow to measure; exchange on even weakly deactivated aromatics such as chlorobenzene cannot be measured in TFA. The bromo derivative (**2**) shows a smaller susceptibility towards bonding than the parent (**1**) as expected in view of electron withdrawal by the halogen.

For compound (**1**) rates were inconveniently slow in the weakest medium so the rate factor between this and 100% TFA was estimated from the factors obtained at higher acidity, which differ only slightly from those for thienothiophenes. This leads to a predicted exchange rate in TFA–HOAc (15:85 v/v) for (**1**) of 0.135×10^{-7}, *cf.* 3.45×10^{-7} s^{-1} for mesitylene.[8] Thus (**1**) is 25.5 times less reactive than mesitylene, *cf.* 370 times less reactive in 100% TFA, the difference being a measure of the attenuation of reactivity through hydrogen bonding. The corrected exchange rate coefficient for (**1**) in 100% TFA becomes $26\,450 \times 10^{-7}$ s^{-1} and since for benzene the exchange rate coefficient[9] is 0.095×10^{-7} s^{-1} the partial rate factor for exchange in (**1**) is 2.78×10^5. Under these conditions, ρ is −8.75,[10] hence σ^+ is −0.62. 1,3λ^{4}δ^2,5,2,4-trithiadiazepine is thus slightly more reactive than the 3-position of thiophene for which the σ^+-value, corrected for hydrogen bonding, is −0.56 (*cf.* −0.913 for the 2-position).[5] Conjugation between a given carbon and the α- and β-sulphurs involves structures (**6**) and (**7**), respectively, formally analogous to the corresponding structures (**8**) and (**9**) for substitution at the α- and β-positions of thiophene. However, greater bond reorganisation from the ground state is required to produce (**6**) than is the case for (**8**), and the sulphurs in (**6**) and (**7**) should be less electron releasing than in thiophene due to the adjacent nitrogens. The observed reactivity of less than the average of the positional reactivities in thiophene is, therefore, reasonable. The reactivity being greater than in benzene is also consistent with *ab initio* calculations (at the STO-3G level) of the net atomic charges at C-6,-7 of −0.189[1] *cf.* −0.063 for benzene.



(**6**) (**7**) (**8**) (**9**)

The corrected rate coefficient for exchange of (**2**) in 100% TFA is $2\,990 \times 10^{-7}$ s^{-1} giving a partial rate factor of 31 500 and σ^+ value of −0.515. (The latter, being at a position *ortho* to bromine, will of course only apply in reactions, like hydrogen exchange, of very low steric requirement). The differences in partial rate factors for (**1**) and (**2**), shows the *o*-bromo substituent to deactivate *ca.* ninefold, which is very much less than the deactivation factor of 37 found across the *ortho* position in benzene,[11] and comparable to the 6.1 deactivation factor across the 1,2-bond in naphthalene (in [1-^{3}H$_1$]-2-bromonaphthalene).[12] The latter differences arise from differences in bond order, the conjugative electron-releasing $+M$ effect of bromine (which counteracts its $-I$ effect) being more effective across a bond of higher order.[12] The effect of bromine in 1,3λ^{4}δ^2,5,2,4-trithiadiazepine is consistent with this explanation since the C–C bond length (1.35 Å) is close to that of the 1,2-bond in naphthalene (1.36 Å) *cf.* 1.40 Å in benzene.

6-*Nitro*-1,3λ^{4}δ^2,5,2,4-*trithiadiazepine* (**3**) *and* 1,3λ^{4}δ^2,5,2,4,6-*Trithiatriazepine* (**4**).—Exchange in these molecules was very slow, and was, therefore, studied using 5 vol% trifluoromethanesulphonic acid in TFA at 70 °C. Some decomposition occurred and initial exchange rate coefficients only were determined as $1\,300 \times 10^{-7}$ and 210×10^{-7} s^{-1}, respectively. The exchange rate coefficient for benzene was $34\,600 \times 10^{-7}$ s^{-1}, so that the partial rate factors are 0.0376 and 0.0061. These are maximum values because although the molecules would be less susceptible to hydrogen bonding (at sulphur) the much stronger acidic conditions would make hydrogen bonding more severe. However, because of the less satisfactory kinetics, no corrections for hydrogen bonding could be applied. The derived σ^+-values (0.16, 0.25) are thus minimum (positive) values.

The deactivation by the *o*-nitro substituent in (**3**) ($> 7.4 \times 10^6$) agrees surprisingly well with the value (2.2×10^7-fold) predicted in benzene (σ^+ for *o*-nitro is 0.84).[13] Greater deactivation is expected in the azepines because of the higher C–C bond order (greater $-M$ effect), and this would almost certainly be the case if hydrogen bonding was taken into account.

Trithiatriazepine is more reactive than 1,3λ^{4}δ^2,5,2,4-trithiadiazepine, as found in bromination and nitration,[2] and our results show that the *o*-aza 'substituent' is slightly more deactivating than *o*-nitro; closely similar effects of these two substituents was earlier predicted from kinetic data in pyrolysis of 1-arylethyl acetates.[6]

Experimental

Preparation of Labelled Compounds.—All compounds were labelled by being heated with a small amount of tritiated water (50 μC cm^{-1} specific activity) and acid as follows: (**1**), TFA, 6 h; (**2**) 5 mol% trifluoromethanesulphonic acid (TMSA) in TFA, 4 h; (**3**) and (**4**), 5 mol% TMSA in TFA, 24 h. Examination of the products by g.l.c. (5% SE30 on 100–120 mesh Chromosorb G at 250 °C, 5′ column) showed no decomposition for either (**1**) or (**2**), but substantial decomposition for both (**3**) and (**4**), thereby confirming the kinetic evidence obtained with the latter of these. The products for both (**3**) and (**4**) were repurified by column chromatography before use.

Attempts to label compound (**5**) led to decomposition which

we judged to be substantial enough to preclude successful kinetic studies by means of hydrogen exchange.

Kinetic Studies.—The general method used for the kinetic studies has been described previously.[14] Compounds (**1**) and (**2**) gave excellent first-order kinetics (linear to at least 95% of reaction). Compounds (**3**) and (**4**) gave plots showing decreasing slope with time due to secondary decomposition, so rate coefficients were determined from the initial 10% of runs only.

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