Electrophilic Aromatic Reactivities *via* Pyrolysis of Esters. Part 21.[1] σ^+ Values for Thiazole: the High Polarisability of Thiazole, and the Effect of Hydrogen Bonding on the Reactivity of *N*-Containing Heterocycles

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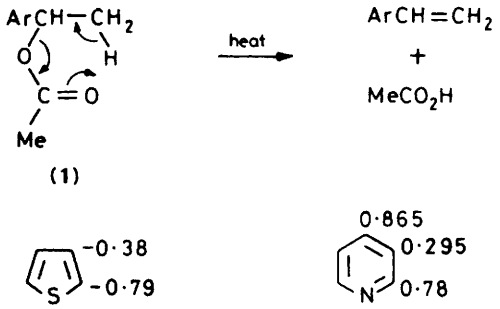
The rates of gas-phase elimination of acetic acid from 1-arylethyl acetates (aryl = thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, or phenyl) have been measured between 633.2 and 698.5 K. The relative rates of pyrolysis at 650 K are: thiazol-2-yl, 0.271; thiazol-4-yl, 0.491; and thiazol-5-yl, 1.104; coupled with the previously determined ρ factor for the reaction (−0.61 at 650 K), this leads to the corresponding σ^+ values 0.93, 0.505, and −0.07. The positional reactivity order, and the reactivity relative to benzene, are correctly predicted by π-electron density calculations. The reactivity of each position is substantially less than in solvolysis of the corresponding 1-aryl-1-chloroethanes, in contrast to the reactivity of thiophene which is closely similar in both pyrolysis and solvolysis reactions. Thiazole is thus much more polarisable than thiophene, and hence particularly susceptible to demands for resonance stabilisation of the respective transition states, the demand being less in the pyrolysis. The difference between the reactivities of the 2-position of thiazole and the corresponding α-position of thiophene (1.72 sigma units) is substantially greater than the difference between the reactivities of the 4-position of thiazole and the β-position of thiophene (0.885 sigma units). This reflects the high 2,3- *vs.* 3,4-bond orders, and consequent variation in the deactivation by the (*ortho*) nitrogen atom. Nitrogen deactivates the 4-position more than it deactivates the 5-position, as expected. By contrast, in solvolysis the 5-position is deactivated more than the 4-position. This latter anomaly is attributed to hydrogen bonding, which is attenuated when the probe group is adjacent to the ring nitrogen atom. This explanation also accounts for the anomalously low reactivity of the 3- and 4-position of pyridine in determination of the electrophilic reactivity *via* solvolysis, as compared with gas-phase data, whereas the reactivity of the 2-position is the same in both reactions.

In previous parts of this series we have used the pyrolysis of 1-arylethyl acetates (**1**), a reaction which proceeds *via* the formation of a partial cation at the 1-carbon atom, and for which ρ is −0.66 at 600 K (−0.61 at 650 K), to determine electrophilic substituent constants for heterocycles. The particular advantage of the reaction (the first to be applied to determining heterocyclic reactivities by the Brown side-chain carbocation technique) is the absence of solvent, so that there are no problems associated either with protonation or with hydrogen bonding; this outweighs the disadvantage of the amount of synthetic work involved as compared with a conventional electrophilic substitution. So far the electrophilic reactivities of all positions of pyridine,[2] furan,[3] thiophene,[3] quinoline,[4] isoquinoline,[5] and benzo[*b*]thiophene,[6] and the 2- and 3-position of benzo[*b*]furan[6] have been determined by this method. The results for pyridine and thiophene, relevant to this study, are shown in terms of σ^+ values in Scheme 1.

The results for thiophene are in excellent agreement with those determined from a number of other reactions,[7] the σ^+ values being at the lower end of the spectrum of values obtained (the variation of data from all studies is *ca.* 0.05 sigma units), which reflects the smaller demand for resonance in the elimination as compared with some other reactions. The pyridine results are in excellent agreement with theoretical predictions,[2] but disagree with those from more recent studies [involving solvolysis of 1-aryl-1-chloropropanes (**2**)], which give the σ^+ values shown in Scheme 2.[8,9]

It is noteworthy that whereas the results for the 2-position in gas-phase and solution studies are in good agreement (and in the latter show the smallest variation amongst the four media used), the values for the 3- and 4-position in the solution

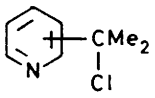


(1)

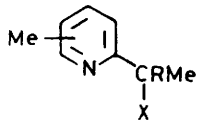
Scheme 1. σ^+ Values from pyrolysis of 1-arylethyl acetates

Scheme 2. σ^+ Values from solvolysis of 1-aryl-1-chloropropanes (the ranges of values for pyridine arise from a range of solvents)

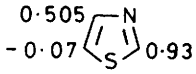
studies are both too positive, relative to the gas phase, by *ca.* 0.25 sigma units. We have previously suggested that this arises because of the very strong hydrogen bonding to which pyridine is subject, which provides additional electron withdrawal from the ring.[10] (The hydrogen chloride by-product in the solvolysis could also partially protonate the nitrogen.) When however the 1-chloropropyl substituent is at the 2-position, the nitrogen may be sufficiently shielded to inhibit hydrogen bonding (particularly in the transition state where the side-chain methyl



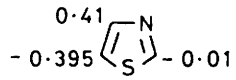
(2)



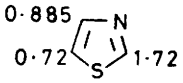
(3) a; R = H, X = OAc
b; R = Me, X = Cl



Scheme 3. σ^+ Values from pyrolysis of 1-thiazolylethyl acetates



Scheme 4. σ^+ Values calculated assuming additivity of aza and thia 'substituent' effects.



Scheme 5. Deactivating effect of the nitrogen in thiazole, in terms of σ^+ values.

groups have to be coplanar with the ring), so the reactivity is not reduced. This view is supported by the fact that in solvolysis of 1-chloro-1-(2-pyridyl)propanes (**3**),[11] methyl substituents at the 4- and 6-position produced markedly different effects, the reactivity being higher when the substituent was at the 6-position (where it would hinder hydrogen bonding). In pyrolysis of the corresponding esters (**3a**),[12] although the 6-methyl group again produced the greater activation, the differential effect between the 4- and 6-position was proportionately smaller (after the difference in ρ factors was taken into account).

There has been only one study of the quantitative electrophilic reactivity of thiazole, which employed the solvolysis of 1-chloro-1-(thiazolyl)ethanes,[13] and yielded the σ^+ values given in Scheme 2. We considered it of interest to obtain the corresponding values in the gas phase to ascertain whether a single set of substituent parameters apply to thiazole, as appears to be approximately true for thiophene, and whether the electronic effects of the heteroatoms are additive, there being no information on this aspect at all in the heteroaromatic literature. We hoped in addition to evaluate the importance of hydrogen bonding, and finally to ascertain the effect of bond fixation which, judged by the effect of substituents in thiophene,[14] is of considerable importance in governing the reactivities of five-membered heterocycles.

Results and Discussion

Rate data are given in the Table; from the ρ factor for the reaction of −0.61 at 650 K, the σ^+ values in Scheme 3 are obtained.

Main features of the results are as follows.

(i) The positional reactivity order is 5 > 4 > 2, as found also in the solvolysis reaction and predicted by m.o. calculations.[15] The latter gave π-electron densities as 1.085(5), 0.971(4), and 0.900(2), and a plot of those values against the σ^+ values is in fact linear (although this may be fortuitous since the point for phenyl lies off the line). Noyce and Fike noted that their solvolysis data did not accord with these predictions[13] (the 4-position being activating) but this is because the solvolysis has a 'later' transition state [see (ii)], and consequently a better correlation with localisation energies might be expected for that reaction (*cf.* results for benzo[*b*]furan and benzo[*b*]thiophene).[6]

(ii) Each position is substantially less reactive than in solvolysis. the discrepancy being particularly large at the 2- and 4-position. The only reasonable explanation for the lower reactivity is that thiazole is particularly susceptible to demands for resonance stabilisation of transition states, *i.e.* it is exceptionally polarisable. The charge found at the α-carbon atom in the transition state for pyrolysis of 1-arylethyl acetates is of course smaller than that at the corresponding position in the solvolysis, though a direct comparison of the need for resonance stabilisation must take into account the lack of solvation in the gas phase. Thus demands for electron release by the aryl group (or substituents within it) will be proportionally greater than would be expected on the basis of charge alone.[16] Nevertheless the demand is less than in the solvolysis (as shown by the data for benzo[*b*]furan and benzo[*b*]thiophene,[6] molecules which are significantly more polarisable than their non-annelated counterparts), so that electron release by sulphur is less able to compensate for the electron withdrawal by nitrogen.

(iii) It is instructive to compare the observed results with those calculated on the basis of additivity of the effects given in Scheme 1, as shown in Scheme 4. Clearly each position is less reactive than calculated. This is in direct contrast to commonly held views regarding substituted benzenes, where the effect of an activating substituent has generally been considered to outweigh the effect of a deactivating one. This generalisation is probably incorrect and may not apply in cases where demand for resonance is low. Indeed, in protiodesilylation, a reaction of low demand for resonance, the overall balance between activation and deactivation by substituents turns out on the side of deactivation.[17]

(iv) Comparison of the data in Schemes 2 and 3 with those in Scheme 4 shows that the observed order of reactivities of the 2- and 4-position is the reverse of that predicted. This follows from the differences in the bond orders in five-membered heterocycles, the 2,3-bond order being substantially greater than the 3,4-bond order. Consequently deactivation by nitrogen across the former will be greater than across the latter (the same effect is evident in isoquinoline[5]). Scheme 5 shows the net deactivating effects of nitrogen (in terms of σ^+ values) calculated assuming that the values for the effect of sulphur, shown in Scheme 1, apply to thiazole.

These data confirm that nitrogen deactivates much more strongly across the 2,3- than the 3,4-bond. The low 3,4-bond order also results in the deactivation by '*ortho*' nitrogen in this direction being not much greater than '*meta*' deactivation, in contrast to the results for pyridine (*cf.* Scheme 1).

(v) If the calculation used to derive the results in Scheme 5 is applied to the solvolysis (using the same σ^+ values for the effect of sulphur since they are largely solvent-independent), the corresponding 2,3-, 3,4-, and 3,5-deactivations by nitrogen (in terms of σ^+ values) are 1.055, 0.37, and 0.615. The former two values confirm the gas-phase results, but the last value is anomalous because the '*meta*' deactivation is now greater than the (3,4-) '*ortho*' deactivation. This suggests that the reactivity of the 5-position in solvolysis is exceptionally low as compared with the 2- and 4-position. It might be argued that the 5-position is not as polarisable as the other two positions, but against this must be set the fact that both the 2- and 5-position are α to sulphur, so that both could be expected to be similarly polarisable.

We consider that hydrogen bonding provides the most probable explanation. When the probe group is at either the 2- or the 4-position, it is able to hinder bonding to the nitrogen, but this will not be the case when it is at the 5-position. This

Table. Pyrolysis of compounds ArCH(Me)OAc

Ar	T/K	10^3k/s^{-1}	log(A/s^{-1})	E/kJ mol^{-1}	Corr. coefft.	k/k_0 at 650 K
Phenyl	633.2	3.83	12.344	178.68	0.999 78	0
	655.1	12.3				
	671.2	27.8				
	688.1	58.4				
	696.5	83.5				
Thiazol-2-yl	633.2	1.03	12.444	187.09	0.999 84	0.271
	655.1	3.35				
	664.5	5.32				
	671.2	7.68				
	688.1	16.9				
	698.5	29.1				
Thiazol-4-yl	636.7	2.29	12.397	183.59	0.999 77	0.491
	651.4	5.02				
	664.5	9.69				
	678.8	18.7				
	698.5	50.1				
Thiazol-5-yl	633.2	4.30	12.240	176.97	0.999 78	1.104
	652.5	12.3				
	655.1	13.2				
	664.5	20.9				
	671.2	29.3				
	688.1	62.7				
	696.5	93.4				

situation therefore parallels exactly that found in pyridine. We do not rule out the possibility of intramolecular hydrogen bonding between nitrogen and the side-chain, which reduces opportunities for intermolecular bonding with the solvent in the solution studies.

Experimental

Kinetic Studies.—The apparatus and general kinetic technique have been described in earlier parts of this series. The present work was carried out using a new reactor, the most significant feature of which is the gold-plated interior surface which minimises surface-catalysed reactions. Full details are described in a recent paper.[18]

Each compound showed excellent and reproducible kinetic behaviour, first-order to > 95% of reaction, and excellent Arrhenius plots (see Table for correlation coefficients). The reaction stoicheiometry was 2.0 ± 0.03 in 10 × $t_{\frac{1}{2}}$ and only vinylthiazoles and acetic acid were detectable as reaction products. The vinylthiazoles are fairly stable; they underwent only very slow secondary decomposition which did not significantly interfere with the primary decomposition. To ensure maximum rigour in analysis of the data, we carried out new runs on 1-phenylethyl acetate, rather than use our existing data; this avoided any possible errors due to thermocouple ageing *etc.*

1-(*Thiazol-2-yl*)*ethyl Acetate.*—1-(Thiazol-2-yl)ethyl alcohol was prepared in 30% yield by the literature method,[13] except that 2-bromothiazole was the starting reagent. The alcohol (1 vol.) was heated under reflux with acetic anhydride (5 vol.) and pyridine (10 vol.) during 2 h. Normal work-up and fractional distillation yielded 1-(*thiazol-2-yl*)*ethyl acetate* (80%), b.p. 65 °C at 1.0 mmHg; n_D^{20} 1.4970 (Found: C, 49.2; H, 5.3; N, 8.3. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2%); δ($CDCl_3$) 7.66 (1 H, d, H-5), 7.22 (1 H, d, H-4), 6.09 (1 H, q, CH), 2.02 (3 H, s, $COCH_3$), and 1.62 (3 H, d, CH_3).

1-(*Thiazol-4-yl*)*ethyl Acetate.*—4-Formylthiazole was prepared according to the literature method,[13] but the following modifications were incorporated to improve the yield.

(i) A substantially higher yield of 1,1,3-tribromoacetone can be obtained from the bromination of acetone,[19] if the crude product is fractionally distilled prior to recrystallisation from light petroleum, thereby removing most of the by-products.

(ii) The decomposition of 4-dibromomethyl-4,5-dihydro-4-hydroxythiazole hydrobromide with sulphuric acid must be continued until the solution is clear, indicating that all the hydrogen bromide has been evolved.

(iii) Heating 4-dibromomethylthiazole with aqueous ethanol does *not* give 4-formylthiazole, as described in the literature,[20] but instead a *ca.* 50:50 mixture of this product and the diethyl acetal. This mixture was converted into the aldehyde δ($CDCl_3$) 10.13 (1 H, s, CHO), 8.98 (1 H, d, H-2), and 8.31 (1 H, d, H-5) by heating with 5% hydrochloric acid during 5 min.

1-(Thiazol-4-yl)ethyl alcohol was prepared in 80% yield, according to the literature method;[13] δ($CDCl_3$) 8.59 (1 H, s, H-2), 7.08 (1 H, s, H-5), 4.82 (1 H, q, CH), and 1.35 (3 H, d, CH_3). Acetylation as above then gave 1-(*thiazol-4-yl*)*ethyl acetate* (93%), b.p. 68 °C at 1 mmHg (Found: C, 49.3; H, 5.1; N, 8.4%); δ($CDCl_3$) 8.79 (1 H, s, H-2), 7.27 (1 H, s, H-5), 6.15 (1 H, q, CH), 2.09 (3 H, s, CH_3), and 1.65 (3 H, d, CH_3).

1-(*Thiazol-5-yl*) *Acetate.*—1-(Thiazol-5-yl)ethyl alcohol was prepared from 2-chlorothiazole according to the literature method.[13] Acetylation as above gave 1-(*thiazol-5-yl*)*ethyl acetate* (55%), b.p. 33 °C at 0.15 mmHg (Found: C, 48.8; H, 5.4; N, 8.05%); δ($CDCl_3$) 8.86 (1 H, s, H-5), 7.90 (1 H, s, H-2), 6.32 (1 H, q, CH), 2.02 (3 H, s, CH_3), and 1.64 (3 H, d, CH_3).

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