The Protonation of Some 5-Substituted Thiophen-2-carboxamides

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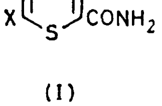
The protonation behaviour at 25 °C in aqueous sulphuric acid solution of some 5-X-thiophen-2-carboxamides ($X = CH_3O, CH_3$, H, Cl, Br, I, and NO_2) has been investigated by u.v. spectrophotometry. pK_{BH^+} Values were calculated by H_A, Bunnett–Olsen, and Cox–Yates methods from experimental absorption curves and by the method of multivariate analysis to separate the effect of protonation from that of the medium. Hammett treatment of the data show a value of $\sigma_{\alpha\text{-}S}$ of 0.63 ± 0.13 indicating that the sulphur atom acts as an electron withdrawing substituent. A plot of pK_{BH^+} against σ is linear and the slope (ρ −1.16) is greater than that of the corresponding benzamides (ρ −0.956) indicating that the thiophen nucleus is more efficient than the benzene ring in relaying the electronic effects of substituents to the reaction centre.

IN the past few years we have carried out kinetic studies with the purpose of comparing side-chain reactivity in the furan and thiophen series with that in the benzene series.[1-5] The differences between the resulting ρ values and those of the corresponding benzenoid side-chain reactions have been discussed in terms of the intensity of transmission of substituent effects.[6,7] The data indicate that heterocyclic rings, depending on the pattern of substitution and the reaction considered, can act as both electron donors and acceptors. The order of magnitude of substituent effects was found to be furan > thiophen > benzene. Tomasik and Johnson [8] pointed out that it is more meaningful to consider the differences in the ρ values as representing the non-additivity of substituent effects. The heteroatom was considered as a substituent which replaces a vinyl group in a benzene ring and able to interact *via* proximity effects with the side-chain, thereby altering its susceptibility to the influence of substituents. By considering the heteroatom as a substituent replacing –CH=CH– in the benzene ring, the substituted heteroaromatic compounds can be regarded as disubstituted benzene derivatives and therefore the substituent constants for the heteroatom can be calculated. The substituent constants so calculated were variable, indicating the possibility of proximity interactions between the heteroatom and the reaction centre and so altering the susceptibility of the side-chain to the influence of substituents.[7b]

Recently we reported the acid dissociation constants of furan- and thiophen-carboxamides in order to study the effects of the heteroatoms on the acidity.[9] We now report the protonation behaviour in aqueous sulphuric acid solution of some 5-substituted thiophen-2-carboxamides (I) to investigate the effect of the heteroatom and to study the transmission of the electronic effects through the thiophen ring.



(I)

$X = H, CH_3, CH_3O$, Cl, Br, I, NO_2

RESULTS AND DISCUSSION

Basicity constants pK_{BH^+} have been calculated at 25 °C using u.v. spectrophotometry and sulphuric acid as solvent. For each compound the value of pK_{BH^+} was obtained from a plot of $\log C_{BH^+}/C_B$ against H_A by consideration of equation (1)[10] where C_{BH^+} and C_B are the concentrations of conjugate acid and base respectively and H_A is the acidity function for amides.[11] Basicity constants have also been calculated using the linear free energy relationship (2) defined by Bunnett and Olsen[12]

$$\log C_{BH^+}/C_B = \log I = -m_A H_A + pK_{BH^+} \qquad (1)$$

$$\log I + H_0 = \phi\,(H_0 + \log C_{H^+}) + pK_{BH^+} \qquad (2)$$

where H_0 is the acidity function for primary aromatic amines.[13] Recently two research groups[14] have suggested essentially the same method for estimating the pK_{BH^+} values of weak bases. We have used the Cox–Yates approach [equation (3)].[14b]

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \qquad (3)$$

Table 1 gives the pK_{BH^+} values of the amides calculated by equations (1)—(3). All the amides closely follow the H_A function, the slopes m of the plots of log I against H_A being 1.04 ± 0.06 except for 5-nitrothiophen-2-carboxamide (m 0.71), as found by Yates and Stevens[15] for *p*-nitrobenzamide (m 0.75). This can be due to difficulties in dealing with the medium effects which are more than usually important with this compound, the spectral changes on protonation being comparatively small (Figure 1A). The agreement among the pK_{BH^+} values by the above methods is good.

The values of $\varepsilon_{max.}$ and $\lambda_{max.}$ are both affected by changes in the medium, independently of the changes produced by protonation. Figure 2A shows the experimental absorption curves at various acid concentrations for 5-methoxythiophen-2-carboxamides, as an example. Since these could substantially affect the slopes of ionization curves on which acidity functions are based, several methods of attempting to correct for these effects have been considered.[16-24]

Recently the u.v. spectra of some compounds in various concentrations of sulphuric acid have been analysed by the method of multivariate analysis to separate the effect of protonation from the generalized medium effect.[10] We have used this method and from the reconstituted curves the ionization ratios at varying acid concentrations were obtained. The reconstituted curves pass through good isosbestic points and ionization ratios calculated from the reconstituted curves, are independent of the wavelengths chosen. From the reconstituted ionization curves the pK_{BH^+} values were calculated by H_A, Bunnett–Olsen, and Cox–Yates methods [equations (1)—(3)]. The results are listed in Table 2. Figures 1B and 2B report the curves reconstituted by multivariate analysis for 5-nitro- and 5-methoxy-thiophen-2-carboxamide, as examples.

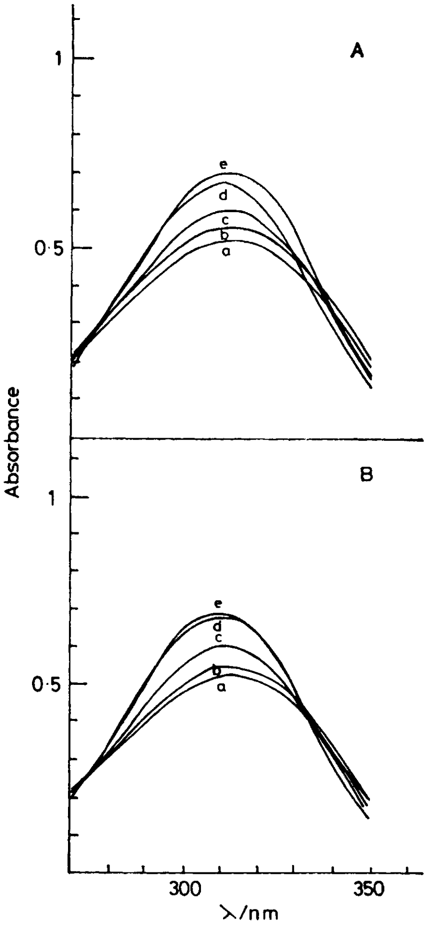


FIGURE 1 Absorption curves of 5-nitrothiophen-2-carboxamide: A, experimental curves; B, reconstituted curves; a, 19.7%; b, 30.2%; c, 40.0%; d, 59.8%; e, 79.7%

TABLE 1

pK_{BH^+} Values of 5-X-thiophen-2-carboxamides calculated by experimental curves

	H_A [a]			Bunnett–Olsen			Cox–Yates		
X	$-$pK_{BH^+}	m_A	r	$-$pK_{BH^+}	ϕ	r	$-$pK_{BH^+}	m^*	r
CH_3O	1.67	1.03	0.997	1.66	0.47	0.990	1.74	0.58	0.996
CH_3	1.78	1.08	0.997	1.80	0.39	0.991	1.87	0.65	0.996
H	2.00	1.10	0.999	1.99	0.40	0.989	2.00	0.60	0.998
I	2.12	1.05	0.993	2.14	0.34	0.979	2.22	0.71	0.998
Br	2.40	1.06	0.997	2.33	0.43	0.996	2.38	0.60	0.996
Cl	2.26	1.04	0.995	2.19	0.48	0.987	2.27	0.56	0.993
NO_2	2.02	0.71	0.992	2.08	0.70	0.996	2.09	0.26	0.989
ρ [b]	-1.25			-1.15			-1.14		
r	0.969			0.980			0.984		

[a] Ref. 11. [b] Except 5-NO_2 derivative.

The results in Table 1 are in good agreement with those of Table 2, except for the 5-nitro-derivative. All the amides follow the H_A function including 5-nitrothiophen-2-carboxamide for which the slope m of the plot of log I against H_A is 1.03. Multivariate analysis separates the effect of protonation from the generalized

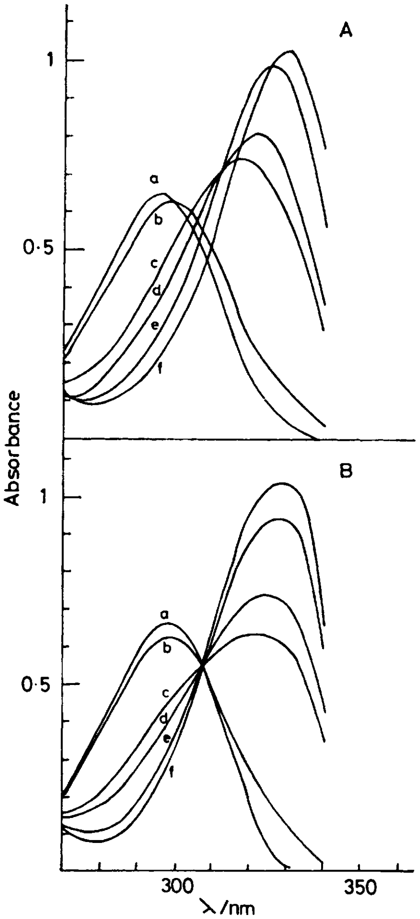


FIGURE 2 Absorption curves of 5-methoxythiophen-2-carboxamide: A, experimental curves; B, reconstituted curves; a, 0%; b, 30.2%; c, 40.0%; d, 44.6%; e, 59.9%; f, 74.8%

medium effect[10] and the fact that, by using the reconstituted absorption curves, the 5-nitro-derivative follows the H_A function strengthens the hypothesis that the experimental absorption curves of 5-nitrothiophen-2-carboxamide, are affected by medium effect. Hence the pK_{BH^+} values of the 5-nitrothiophen-2-carboxamide calculated from the experimental absorption curves are meaningless.

The results here reported show that in thiophen-2-carboxamides the basicity is lower than in benzamides indicating that the heteroatom behaves as an electron-withdrawing substitutent. By considering the heteroatom as a substituent which replaces CH=CH in the benzene ring, 5-substituted thiophen-2-carboxamides can be regarded as disubstituted benzene derivatives and therefore the substituent constant for the sulphur atom in the thiophen ring ($\sigma_{\alpha\text{-S}}$) can be calculated from equation (4)[25] where pK_a (-1.45) and ρ (-0.956) are,

$$\sigma_{\alpha\text{-S}} = \frac{pK_0 - pK_a - \sigma_X}{\rho} \qquad (4)$$

respectively, the intercept and the slope of the Hammett plot of the corresponding substituted benzamides[15] calculated by equation (1) using the H_A function acidity revised by Edward,[11] except for *p*-nitrobenzamide; pK_a is the value for 5-substituted thiophen-2-carboxamide, calculated from experimental absorption curves by using the H_A acidity function (Table 1). For the 5-nitro-derivative the pK_a value is that calculated from reconstituted curves (Table 2); σ_X is the substituent constant for the X substituent in 5-substituted derivatives.

The calculated $\sigma_{\alpha\text{-S}}$ constants are 0.50 for 5-CH_3O, 0.51 for 5-CH_3, 0.57 for 5-H, 0.62 for 5-Cl, 0.76 for 5-Br, 0.52 for 5-I, and 0.49 for 5-NO_2. The $\sigma_{\alpha\text{-S}}$ values here reported are almost constant indicating that there are no proximity interactions between the heteroatom and the reaction centre.[8] The positive $\sigma_{\alpha\text{-S}}$ value indicates net electron withdrawal due to the inductive and resonance polar effects of the heteroatom at the α-position.[9]

TABLE 2

pK_{BH^+} Values of 5-X-thiophen-2-carboxamides calculated by reconstituted curves

	H_A[a]								
X	$-pK_{BH^+}$	m_A	r	$-pK_{BH^+}$	ϕ	r	$-pK_{BH^+}$	m*	r
CH_3O	1.53	0.95	0.996	1.58	0.51	0.970	1.64	0.52	0.985
CH_3	1.57	1.00	0.997	1.69	0.42	0.985	1.73	0.60	0.996
H	1.88	0.98	0.997	1.88	0.50	0.993	1.94	0.52	0.992
I	1.98	1.05	0.996	2.11	0.38	0.980	2.13	0.64	0.996
Br	2.36	1.04	0.995	2.25	0.44	0.989	2.34	0.61	0.998
Cl	2.27	1.03	0.994	2.16	0.50	0.987	2.25	0.54	0.991
NO_2	2.66	1.03	0.962	2.46	0.50	0.939	2.54	0.51	0.950
ρ	-1.16			-0.87			-0.91		
r	0.950			0.953			0.949		

[a] Ref. 11.

The plots of pK_{BH^+} at 25 °C, calculated by the above methods, against the Hammett σ constants are linear and the results are listed in Tables 1 and 2. Figure 3 shows a plot of pK_{BH^+} at 25 °C, calculated by the H_A acidity function, against the σ constants, as an example. The Hammett equation has been applied by considering the 2- and 5-positions as *para*-like and then using σ_p values.[25] The larger ρ value for 5-substituted thiophen-2-carboxamides (-1.16) than for benzamides (-0.956) indicates that the thiophen nucleus is more efficient than benzene in relaying the electronic effects of the substituent to the reaction centre, as found for other side-chain reactions.[26-34]

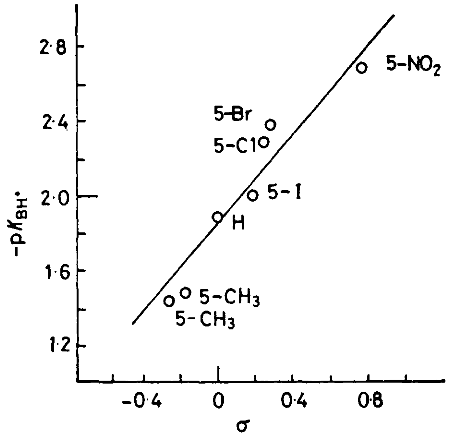


FIGURE 3 Plot of $-pK_{BH^+}$ at 25 °C calculated by the H_A function acidity against σ constants

EXPERIMENTAL

Materials.—Thiophen-2-carboxamide,[35] 5-methyl-,[35] 5-methoxy-,[36] 5-chloro-,[35] 5-bromo-,[37] 5-iodo-,[38] and 5-nitrothiophen-2-carboxamide[35] were prepared as reported.

pK_{BH^+} *Measurements*.—Concentrated sulphuric acid was standardized against standard sodium hydroxide, using Methyl Orange as indicator. Acid solutions of various concentrations were made up by diluting concentrated sulphuric acid with distilled water, by weight, to give the required acidity. Hydrolysis of the amides is negligible during the time required to measure spectra. The spectra of acid solutions of each amide were recorded on a Hitachi EPS 3T spectrophotometer. Plots of ε in the region of $\lambda_{max.}$ (BH^+) against H_A were examined, and the wavelength which gave the smoothest sigmoid curve was chosen to calculate the ionization ratios.[39] pK_{BH^+} Values have been calculated from equations (1)—(3). The absorption curves have been reconstituted by the method of multivariate analysis, using the computer program described in ref. 10.

The ionization ratios and $\mathrm{p}K_{\mathrm{BH^+}}$ values were then calculated from the reconstituted spectra by equations (1)—(3).

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