# Protonation of Some 3-, 4-, and 5-Substituted Thiophen-2-carboxamides †

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The protonation behaviour at 25 °C in aqueous sulphuric acid solution of some 3-, 4-, and 5-substituted thiophen-2-carboxamides has been investigated by u.v. spectrophotometry. pK_{BH^+} Values were calculated by H_A and Bunnett–Olsen methods using the multivariate analysis. A positive $\sigma_{\alpha-s}$ value was obtained indicating that the sulphur atom acts as an electron-withdrawing substituent. Plots of pK_{BH^+} of 4- and 5-substituted thiophen-2-carboxamides and 3-substituted derivatives against σ were linear with the slope +1.10 and +1.28, respectively. A $\rho_o/\rho_{m,p}$ ratio higher than unity (1.16) has been observed indicating a larger transmission of electronic effects between the 2- and 3-positions of the thiophen ring than between the 2- and 4- or 5-positions.

WE have recently studied the protonation of some heterocyclic carboxamides.[1] In particular, the behaviour of furan-2- and -3- or thiophen-2- and -3-carboxamides and their N-methyl and NN-dimethyl derivatives was investigated to provide information on the effect of the heteroatoms on basicity.[1a] The results have been compared with those of the corresponding benzene derivatives and the following sequence of basicity was obtained: 3-furyl ~ 3-thienyl ~ phenyl > 2-furyl ~ 2-thienyl.

We have investigated the transmission of electronic effects of substituents in five-membered ring derivatives.[1,2] Moreover, in the case of *ortho*-like substituted thiophen compounds, we have shown that there is the possibility of obtaining linear Hammett-type *ortho*-correlations.[3] We now report data for the protonation of amides (I) in aqueous sulphuric acid solution at 25 °C.

$$X\text{---}\underset{S}{\boxed{}}\text{---}CONH_2$$
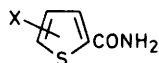
(I)

a ; X = 5 - OMe h ; X = 5 - Br   o ; X = 3 - Me
b ; X = 5 - SMe i ; X = 4 - Br   p ; X = 3 - F
c ; X = 5 - Me   j ; X = 5 - Cl   q ; X = 3 - Br
d ; X = 5 - Et   k ; X = 5 - NO₂ r ; X = 3 - I
e ; X = 4 - Me   l ; X = 5 - SO₂Me s ; X = 3 - SOMe
f ; X = H   m ; X = 3 - OMe t ; X = 3 - SO₂Me
g ; X = 5 - I   n ; X = 3 - SMe

RESULTS AND DISCUSSION

The protonation behaviour of amides (I) has been investigated at 25 °C in aqueous sulphuric acid solution by u.v. spectrophotometry. pK_{BH^+} Values were calculated by H_A[4,5] and Bunnett–Olsen[6] methods using multivariate analysis[7] and the data are listed in Tables 1 and 2.

All the amides closely follow the H_A function, the slopes m of plots of log I against H_A being 1.00 ± 0.10. This is so for thiophencarboxamides substituted with strong electron-withdrawing groups (Ik, l, t) at variance with results for 4-nitrobenzamide, for which a low m_A value

† Presented to the 2nd European Symposium on Organic Chemistry, Stresa, 1981.

TABLE 1

Ionization data at 25 °C in sulphuric acid for 4- and 5-X-thiophen-2-carboxamides

| Compd. | H_A [a] | | | Bunnett–Olsen | | |
	$-pK_{BH^+}$	m_A	r	$-pK_{BH^+}$	ϕ	r
(Ia) [b]	1.53	0.95	0.996	1.58	0.51	0.970
(Ib) [b]	1.80	0.97	0.989	1.82	0 48	0.987
(Ic)	1.57	1.00	0.997	1.69	0.42	0.985
(Id)	1.68	0.98	0.991	1.72	0.46	0.997
(Ie)	1.79	1.01	0.998	1.82	0.46	0.997
(If) [b]	1.88	0.98	0.997	1.88	0.50	0.993
(Ig) [b]	1.98	1.05	0.996	2.11	0.38	0.980
(Ih) [b]	2.36	1.04	0.995	2.25	0.44	0.989
(Ii)	2.40	1.01	0.996	2.38	0.49	0.993
(Ij) [b]	2.27	1.03	0.994	2.16	0.50	0.987
(Ik) [b]	2.66	1.03	0.962	2.46	0.50	0.939
(Il)	2.52	0.99	0.992	2.49	0.48	0.993

$\rho \pm s_\rho$	+1.10 ± 0.11			+0.91 ± 0.08		
$i \pm s_i$	+1.87 ± 0.04			+1.89 ± 0.03		
r	0.957			0.962		
c.l.	>99.9%			>99.9%		

[a] Ref. 5. [b] Ref. 1b.

TABLE 2

Ionization data at 25 °C in sulphuric acid for 3-X-thiophen-2-carboxamides

| Compd. | H_A [a] | | | Bunnett–Olsen | | |
	$-pK_{BH^+}$	m_A	r	$-pK_{BH^+}$	ϕ	r
(Im)	1.33	0.90	0.998	1.48	0.50	0.988
(In)	1.88	1.06	0.993	2.00	0.41	0.990
(Io)	1.80	1.00	0.998	1.83	0.47	0.988
(If) [b]	1.88	0.98	0.997	1.88	0.50	0.993
(Ip)	1.94	0.95	0.993	2.04	0.54	0.998
(Iq)	2.36	1.02	0.999	2.39	0.48	0.998
(Ir)	2.41	1.06	0.998	2.39	0.47	0.998
(Is)	2.40	0.96	0.989	2.38	0.49	0.988
(It)	2.74	1.10	0.987	2.67	0.45	0.984

$\rho \pm s_\rho$	+1.28 ± 0.19			+1.10 ± 0.17		
$i \pm s_i$	+1.91 ± 0.06			+1.97 ± 0.05		
r	0.931			0.928		
c.l.	>99.9%			>99.9%		

[a] Ref. 5. [b] Ref. 1b.

has been reported (m_A 0.75).[8] The correlation coefficients for the Bunnett–Olsen plots are satisfactory and the ϕ values are in the expected range for amides.[9] The agreement among the pK_{BH^+} values by the above methods is good.

We have already published results on linear free energy

correlations of some 5-X-thiophen-2-carboxamides (X = CH₃O, CH₃, H, I, Br, Cl, NO₂); [1b] we have now extended the investigation to other substituents (X = CH₃S, C₂H₅, and SO₂CH₃) and also to some 4-X-thiophen-2-carboxamides (X = CH₃ and Br). The Hammett plots are linear using pK_{BH^+} obtained by both H_A and Bunnett–Olsen methods with intercept values practically coincident with the experimental pK_{BH^+} value for (If) and the results are listed in Table 1. The Hammett equation has been applied by considering the 2- and 5-positions as para-like and the 2- and 4-positions as meta-like and then using σ_p and σ_m values. [10]

The data collected show that the basicity of thiophen-2-carboxamides is lower than that of the corresponding benzamides indicating that the heteroatom behaves as an electron-withdrawing substituent. By considering the heteroatom as a substituent which replaces –CH=CH– in the benzene ring, 4- and 5-substituted thiophen-2-carboxamides can be regarded as disubstituted benzene derivatives and the substituent constant for the sulphur atom in the benzene ring ($\sigma_{\alpha-S}$) has been calculated from equation (1) [10] where pK_0 (−1.45) and ρ (+0.956) are,

$$\sigma_{\alpha-S} = \frac{pK_0 - pK}{\rho} - \sigma_X \qquad (1)$$

respectively, the intercept and the slope of the Hammett plot of the corresponding benzamides [8] obtained using the H_A acidity function revised by Edward, [5] except for p-nitrobenzamide; pK_a is the value for 5- or 4-substituted thiophen-2-carboxamides, calculated by the H_A acidity function. σ_X Is the substituent constant for the X substituent in 4- and 5-substituted derivatives. The positive $\sigma_{\alpha-S}$ values, listed in Table 3 (mean value 0.46,

TABLE 3

$\sigma_{\alpha-S}$ Values calculated for 4- and 5-X-thiophen-2-carboxamides

X	$\sigma_{\alpha-S}$
5-OCH₃	0.35
5-SCH₃	0.37
5-CH₃	0.30
5-C₂H₅	0.39
4-CH₃	0.43
H	0.45
5-I	0.37
5-Br	0.72
4-Br	0.60
5-Cl	0.63
5-NO₂	0.49
5-SO₂CH₃	0.40

standard deviation 0.13), show that there are no proximity interactions between the heteroatom and the reaction centre [11] and indicate net electron withdrawal due to the inductive and resonance polar effects of the heteroatom on the α-position. [1a,b,12]

In connection with our previous researches on linear free energy ortho-correlations in thiophen derivatives we have also studied the behaviour of some ortho-like substituted thiophencarboxamides (Im—t). As expected also in this case the pK_{BH^+} obtained are linearly correlated with σ_H. This is in agreement with the results previously obtained from studies of the behaviour of

various 3-substituted thiophen-2-carboxylic acids [13,14] and of some derivatives [15,16] which have shown that, at variance with the results for six-membered systems, [17] five-membered ring compounds give linear ortho-correlations. [18–20]

The susceptibility constants obtained for the ortho-like substituent compounds can be compared with those for meta- and para-like substituted thiophen-2-carboxamides.

The ratio $\rho_o/\rho_{m,p}$ (1.16) obtained is higher than unity and confirms the larger transmission of electronic effects between the 2- and 3-positions in the thiophen ring than between the 2- and 4- or 5-positions, found for other side-chain reactions (acidity of thiophen-2-carboxylic acids, [13] hydrolysis of methyl esters of thiophen-2-carboxylic acids, [15] anilinodechlorination of 2-thenoyl chlorides, [16] and esterification of thiophen-2-carboxylic acids with diazodiphenylmethane [14]).

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