The Protonation of Furan- and Thiophen-carboxamides

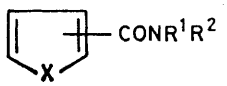
By **Gaetano Alberghina, Salvatore Fisichella,** and **Giuseppe Musumarra,** Institute of Industrial Chemistry of the University, Viale Andrea Doria 6, 95125 Catania, Italy

The protonation behaviour in aqueous sulphuric acid solution of various furan- and thiophen-carboxamides has been investigated by u.v. spectrophotometry. The pK_{BH^+} values, calculated using the H_A acidity function and the Bunnett–Olsen linear free energy relationship, indicate the lower basicity of furan- and thiophen-2-carboxamides with respect to that of benzamides and of the 3-derivatives. The question of the site of protonation is also discussed.

FURYL and thienyl groups may act as electron-donating or electron-withdrawing substituents. In the acid-catalysed rearrangement of substituted allyl alcohols [1] they are electron-donating. The carboxylic acids of furan and thiophen are stronger than benzoic acid indicating the inductive electron-withdrawing effect of the heteroaromatic nuclei.[2] In the esterification of the 2- and 3-furoic acids,[3] in the acid-catalysed hydrolysis of furan- and thiophen-carboxylic esters,[4] and in the alkaline hydrolysis of 2- and 3-thenoates and 3-furoates the furyl and thienyl groups are both electron-donating, whereas in the alkaline hydrolysis of 2-furoates the furyl group is electron-withdrawing.[4-7] In the solvolysis of 1-arylethyl acetates [8] and of *p*-nitrobenzoates [9] and in the isomerization of *cis*-2-styrylthiophen in aqueous sulphuric acid [10] the furan and thiophen nuclei are electron-donating, whereas in the rearrangement of di-2-thienyl diketone the thienyl group is electron-withdrawing.[11]

We have been studying the kinetics of the reaction of thenoyl [12,13] and furoyl chlorides [14,15] with anilines, chloroacetyl-furans and -thiophens with triethyl phosphite,[16] and the basic [17] and acidic hydrolysis of 2- and 3-furanilides and 2- and 3-thenanilides [18] with the aim of studying the influence of the five-membered heterocyclic rings on the reactivity of the side-chain. The results showed that the thienyl group is electron-donating in the reaction of acid chlorides with anilines and of chloroacetylthiophens with triethyl phosphite and in the acid hydrolysis of anilides, but is electron-withdrawing in the basic hydrolysis of anilides. The furyl group is electron-withdrawing in the reaction of 2-furoyl chloride with aniline and of 2-chloroacetylfuran with triethyl phosphite and in the basic hydrolysis of anilides.

Recently we reported the acid dissociation constants of thiophen- and furan-sulphonamides in order to study the effects of the heteroatoms and other substituents on their acidity.[19] We now report the protonation behaviour in aqueous sulphuric acid solution of the furan- and thiophen-carboxamides (1)—(4) to investigate the effect of



(1) X = α-O (3) X = α-S
(2) X = β-O (4) X = β-S
a; $R^1 = R^2 = H$
b; $R^1 = H$; $R^2 = Me$
c; $R^1 = R^2 = Me$

the heteroatoms by means of pK_a values expressed in terms of acidity functions. We also report the ^{13}C n.m.r. spectra of *N*-methylbenzamide at various acidities with regard to the protonation site.

RESULTS AND DISCUSSION

The ionization data at 25 °C in sulphuric acid for the amides (1)—(4) and for benzamide, determined by the H_A acidity function [20] and by the Bunnett–Olsen linear free energy relationship (L.F.E.R.),[21] are reported in Table 1. These amides follow closely the appropriate

TABLE 1

Ionization data at 25 °C in sulphuric acid determined by acidity function (H_A) and Bunnett–Olsen L.F.E.R. methods

		Acidity function		L.F.E.R.		
Compound	λ/nm	$-pK_{BH^+}$ [a]	$-\frac{d \log I}{d H_A}$	ϕ	$-pK_{BH^+}$	r
(1a)	273	1.84 [b]	1.06	0.40	1.84	0.992
(1b)	270—255 [c]	1.86	1.00	0.45	1.80	0.994
(1c)	273	1.40	1.30	0.22	1.65	0.992
(2a)	260—235 [c]	1.56	0.98	0.47	1.48	0.994
(2b)	257	1.67	1.01	0.49	1.51	0.993
(2c)	255—220 [c]	0.90	0.97	0.40	0.94	0.983
(3a)	293	1.94	1.10	0.40	1.99	0.989
(3b)	290	2.03	1.09	0.40	2.09	0.998
(3c)	288	1.86	0.88	0.63	1.40	0.998
(4a)	255	1.52	1.12	0.35	1.59	0.985
(4b)	255	1.66	1.02	0.42	1.65	0.991
(4c)	253	1.32	1.01	0.37	1.40	0.953
Benzamide	247	1.65 [d]	1.03	0.42	1.68	0.997

[a] H_A (half protonation) +0.2, ref. 20*b*, p. 203. [b] Lit.,[20b] 1.90. [c] Method of C. T. Davies and T. A. Geissman, *J. Amer. Chem. Soc.*, 1654, **76**, 5507. [d] Lit.,[24] 1.64.

acidity function H_A, the slopes of the plots of log I *vs.* H_A being very close to unity, apart from that for the *NN*-dimethyl derivative (1c) whose pK_{BH^+} value has no thermodynamic significance, its slope deviating significantly from unity.[22] The correlation coefficients for the Bunnett–Olsen plots are satisfactory and the ϕ values are in the expected range for amides and *N*-methylamides, the calculated value for benzamide coinciding with the literature value.[23]

The basicity of the *N*-methyl derivatives is similar to that of the corresponding amides, while that of the *NN*-dimethyl derivatives is higher, in agreement with the corresponding benzamide analogues.[22,24]

The pK_{BH^+} values, calculated using both methods, follow roughly the same sequence, apart from (1c) whose anomalous behaviour has already been noted. The following basicity sequence for the heteroaromatic rings can be written, taking into account the magnitude of experimental errors: 3-furyl ~ 3-thienyl ~ phenyl > 2-furyl ~ 2-thienyl. The main feature of this sequence is the similar basicity of furan- and thiophen-2-carboxamides, which is lower than that of the 3-derivatives and of the benzene analogues. This finding, verified in all three series using H_A, and in the amide and *N*-methyl series using the Bunnett–Olsen linear free energy relationship, seems unlikely to be due to experimental errors.

The effect of the heteroatoms in five-membered rings may be evaluated in terms of σ_{het} constants for the heteroatoms defined by equation (1),[25] where pK_0 and ρ

$$\sigma_{het} = (pK_0 - pK_a)/\rho \qquad (1)$$

are respectively the intercept and the slope of the Hammett plot including the data for the corresponding substituted benzene derivatives. The pK_a values of substituted benzamides [20b, 22] are satisfactorily correlated with σ constants ($r = 0.982$, $\rho = -1.03 \pm 0.19$, $pK_0 = -1.56 \pm 0.07$, 99% confidence limit). The evaluated σ constants for the heteroatoms are: $\sigma_{\alpha\text{-}O} = 0.27$, $\sigma_{\alpha\text{-}S} = 0.37$, $\sigma_{\beta\text{-}O} = 0.00$, and $\sigma_{\beta\text{-}S} = -0.04$.

The positive $\sigma_{\alpha\text{-}O}$ and $\sigma_{\alpha\text{-}S}$ values indicate a net electron withdrawal due to the inductive and resonance polar effects of the heteroatom at the α-position, although this effect is smaller than in the ionization of carboxylic acids from which more positive σ values can be derived.[2]

Site of Protonation.—The question of the site of protonation of amides has been widely debated and reviewed.[20b,26-29] Recent literature evidence in favour of predominant *O*-protonation under various conditions [30-32] has been accompanied by the postulation of a tautomeric change from the *N*-protonated form in moderately acidic solutions to the *O*-protonated form in concentrated acids.[33]

The ^{13}C n.m.r. spectra of amides and their protonation shifts can provide information on the protonation site. ^{13}C N.m.r. evidence for *O*-protonation of *NN*-dimethylformamide has been reported.[34]

The ^{13}C n.m.r. spectra of *N*-methylbenzamide in deuteriochloroform and in four sulphuric acid–deuterium oxide mixtures of different acidity are reported in Table 2.

TABLE 2

Carbon-13 n.m.r. chemical shifts of *N*-methylbenzamide in $CDCl_3$ [a] and in H_2SO_4–D_2O [b]

Solvent	C=O	C-1	C-2	C-3	C-4	Me
$CDCl_3$	168.4	134.6	126.9	128.4	131.2	26.8
9.2 [c]	171.9	133.9	127.7	129.5	132.8	27.4
16 [c]	172.2	133.3	127.8	129.6	133.1	27.8
35 [c]	173.2	130.3	128.4	130.0	134.5	28.9
71 [c]	173.7	129.6	128.7	130.3	135.1	29.4

[a] In p.p.m. downfield from Me_4Si internal standard. [b] In p.p.m. downfield from Me_4Si external standard. [c] % H_2SO_4 in D_2O (w/w).

The spectra in deuteriochloroform are consistent with those of benzamide and *NN*-dimethylbenzamide.[35] On increasing the acidity of the medium, the carbonyl carbon atom as well as the methyl group, are deshielded, while the *ipso* carbon atom is significantly shielded. These protonation shifts are in complete agreement with those reported in a recent study,[36] which includes INDO calculations, indicating that the total valence electron density of the carbonyl C atom is diminished by *O*-protonation in the case of *N*-ethylpropionamide. Our data seem then to be consistent with *O*-protonation.

EXPERIMENTAL

Materials.—2-Furamide,[37] *N*-methyl-2-furamide,[38] *NN*-dimethyl-2-furamide,[38] 3-furamide,[39] *N*-methyl-3-furamide,[40] *NN*-dimethyl-3-furamide,[41] thiophen-2-carboxamide,[42] *N*-methylthiophen-2-carboxamide,[43] *NN*-dimethylthiophen-2-carboxamide,[44] and thiophen-3-carboxamide [45] were prepared as reported. The other amides were prepared by bubbling the amine through an anhydrous ether solution of the acid chloride at −10 °C. The mixture was filtered, the filtrate evaporated, and the residue recrystallized from ether: N-*methylthiophen-3-carboxamide* (4b) had m.p. 114—116 °C (Found: C, 50.85; H, 5.0; N, 9.8; S, 22.7. C_6H_7NOS requires C, 51.0; H, 5.0; N, 9.9; S, 22.70%); NN-*dimethylthiophen-3-carboxamide* (4c) had m.p. 45 °C (Found: C, 54.1; H, 5.7; N, 9.0; S, 20.6. C_7H_9NOS requires C, 54.2; H, 5.85; N, 9.0; S, 20.65%).

pK_a *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. 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^+) or $\Delta\varepsilon$ at two wavelengths against H_A were examined, and the wavelength which gave the smoothest sigmoid curve was chosen to calculate the ionization ratios.[20a] H_A Values at half protonation $(H_A)_{1/2}$ were evaluated by plotting log I *vs.* H_A[20a] and the ϕ parameter (slope) and the pK_{BH^+} (intercept) from the plot of (log I + H_0) *vs.* (H_0 + log c_{H^+}).[21]

N.m.r. spectra.—^{13}C N.m.r. spectra were recorded on a JEOL FX-100 spectrometer at 25.05 MHz, at 28 °C for *ca.* 1 M solutions in deuteriochloroform using tetramethylsilane as internal standard. For sulphuric acid–deuterium oxide mixtures the temperature increased during accumulation, owing to power absorption from the decoupler, the concentration varied in the range 0.4—0.7M, and tetramethylsilane was used as external standard. Typical conditions

were: 5 kHz width, 8 k data giving an effective resolution of 0.05 p.p.m.

We thank C.N.R. (Rome) for financial support.

[9/134 *Received*, 29*th January*, 1979]

REFERENCES

[1] E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 1952, 4158.
[2] G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 242.
[3] H. A. Smith, J. B. Conley, and W. H. King, *J. Amer. Chem. Soc.*, 1951, **73**, 4633.
[4] P. A. Ten Thije and M. J. Janssen, *Rec. Trav. chim.*, 1965, **84**, 1169.
[5] E. Imoto, Y. Otsuji, T. Hirai, and H. Inoue, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 1956, **77**, 804, 809.
[6] S. Oae and C. C. Price, *J. Amer. Chem. Soc.*, 1957, **79**, 2457.
[7] Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi*, 1959, **80**, 1293.
[8] E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Amer. Chem. Soc.*, 1969, **91**, 7381.
[9] D. S. Noyce and G. V. Kaiser, *J. Org. Chem.*, 1969, **34**, 1008; D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *ibid.*, 1972, **37**, 2615; D. S. Noyce and H. J. Pavez, *ibid.*, p. 2620.
[10] D. S. Noyce, C. A. Lipinski, and G. M. Loudon, *J. Org. Chem.*, 1970, **35**, 1718.
[11] G. P. Nilles and R. D. Schuetz, *J. Org. Chem.*, 1971, **36**, 2489.
[12] A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, 1973, **38**, 32.
[13] A. Arcoria and S. Fisichella, *J. Org. Chem.*, 1973, **38**, 3774.
[14] A. Arcoria, S. Fisichella, G. Scarlata, and D. Sciotto, *J. Org. Chem.*, 1974, **39**, 3025.
[15] A. Arcoria and S. Fisichella, *Gazzetta*, 1973, **103**, 813.
[16] A. Arcoria, S. Fisichella, E. Maccarone, and G. Scarlata, *Gazzetta*, 1975, **105**, 547.
[17] A. Arcoria, S. Fisichella, S. Occhipinti, and D. Sciotto, *Ann. Chim. (Italy)*, 1974, **64**, 95.
[18] A. Arcoria, S. Fisichella, S. Occhipinti, and D. Sciotto, *Gazzetta*, 1977, **107**, 213.
[19] A. Ballistreri, E. Maccarone, and G. Musumarra, *J.C.S. Perkin II*, 1977, 984.
[20] (*a*) K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1956; (*b*) R. B. Homer and C. D. Johnson, 'The Chemistry of Amides,' ed. J. Zabicky, Wiley–Interscience, New York, 1970, ch. 3, p. 187.
[21] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1899.
[22] K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1967, **43**, 529.
[23] A. Levi, G. Modena, and G. Scorrano, *J. Amer. Chem. Soc.*, 1974, **96**, 6585.
[24] C. A. Bunton, S. J. Farber, A. G. J. Milbank, C. J. O'Connor, and T. A. Turney, *J.C.S. Perkin II*, 1972, 1869.
[25] P. Tomasik and C. D. Johnson, *Adv. Heterocyclic Chem.*, 1976, **20**, 1.
[26] A. R. Katritzky and R. A. Y. Jones, *Chem. and Ind.*, 1961, 722.
[27] C. J. O'Connor, *Quart. Rev.*, 1970, **24**, 553.
[28] M. Liler, 'Reaction Mechanisms in Sulphuric Acid,' Academic Press, London, 1971, ch. 3.
[29] C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 706.
[30] H. Benderly and K. Rosenheck, *J.C.S. Chem. Comm.*, 1972, 179.
[31] R. B. Martin, *J.C.S. Chem. Comm.*, 1972, 793.
[32] C. R. Smith and K. Yates, *Canad. J. Chem.*, 1972, **50**, 771.
[33] M. Liler, *J.C.S. Perkin II*, 1974, 71.
[34] R. A. McClelland and W. F. Reynolds, *J.C.S. Chem. Comm.*, 1974, 824.
[35] R. G. Jones and J. M. Wilkins, *Org. Magnetic Resonance*, 1978, **11**, 20.
[36] S. Berger, *Tetrahedron*, 1978, **34**, 3133.
[37] J. A. Blauchette and E. V. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2098.
[38] R. I. Meltzer, A. D. Lewis, and J. A. King, *J. Amer. Chem. Soc.*, 1955, **77**, 4062.
[39] K. Galuszko and J. T. Wrobel, *Roczniki Chem.*, 1964, **38**, 511 (*Chem. Abs.*, 1964, **61**, 10,640d).
[40] H. Horstmann, H. Woeweber, and K. Meng, B.P. 1,031,916 (1966) (*Chem. Abs.*, 1969, **70**, P 19,915u).
[41] M. Robba, M. C. Zaluski and B. Rognes, *Compt. rend.* (*C*), 1967, **264**, 413.
[42] J. A. Blauchette and E. V. Brown, *J. Amer. Chem. Soc.*, 1951, **73**, 2779.
[43] S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Amer. Chem. Soc.*, 1959, **81**, 3728.
[44] U. Michael and A. B. Hornfeldt, *Tetrahedron Letters*, 1970, **60**, 5219.
[45] E. E. Compaigne and R. C. Burgeois, *J. Amer. Chem. Soc.*, 1953, **75**, 2702.