The Protonation of Some 5-Substituted 3-Nitro-2-*NN*-dimethylaminothiophens

Paolo De Maria, Giovanni Consiglio, Caterina Arnone, and Domenico Spinelli *
Cattedra di Chimica Organica, Istituto di Scienze Chimiche, Facoltà di Farmacia, Università di Bologna, Via Zanolini 3, Bologna 40126, Italy

The title reaction has been studied in aqueous perchloric acid. The experimental $\mathrm{p}K_{\mathrm{BH}^+}$ values obtained according to the Hammett, Bunnett and Olsen, and Yates and Cox methods give good Hammett correlations with 'thiophen' σ^- values. A comparison with the susceptibility constants measured for some series of *NN*-dimethylanilines has been made and the influence of the hyper-*ortho* relation in determining the $\mathrm{p}K_{\mathrm{BH}^+}$ values of the title compounds has been discussed.

The validity and the application of linear free energy relationships have been extended to the study of equilibrium processes and of reactivities of several heterocyclic compounds.[1] In five-membered ring systems containing one heteroatom the 2,5- and 2,4-relations have been regarded as *para*- and *meta*-like and this has enabled the use of the Hammett equation or of more sophisticated relationships.[1]

Our research group has widely used these treatments to study side-chain as well as ring reactions especially in thiophen derivatives.[2–4] In connection with our interest in any facet of S_NAr processes in thiophen compounds we have studied the application of Hammett-type relationships to piperidino-[3] and anilino-substitutions [4] of some 2-L-3-nitro-5-X-thiophens using as substituent constants the so-called σ^- values. In fact these values, since they are defined from acidity constants of substituted phenols [5,6] and anilines,[5,7] have been largely used in studies of S_NAr reactivities on the basis of the resemblance of the through-resonance interactions in anilines or in phenoxide anions and in transition states or σ-complexes of S_NAr reactions. Using the 'benzene' σ^- values and the Brown and Stock method [8] we have defined 'thiophen' σ^- values for both nucleophilic aromatic piperidino-[3] and anilino-substitutions.[4]

In order to test the general validity of these substituent constants we have determined the protonation constants of some 5-substituted 3-nitro-2-*NN*-dimethylaminothiophens (Ia—i) in aqueous perchloric acid. This reaction can be regarded as a good reference reaction to check thiophen σ^- values, in that the transmission of substituent effects in (I) is similar to that present in substituted anilines and *NN*-dialkylanilines.

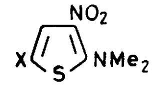
Results

Acid dissociation constants, $\mathrm{p}K_{\mathrm{BH}^+}$, have been determined spectrophotometrically at 25 °C in aqueous solutions of perchloric acid.

Protonation data have been analysed by three different methods (see Table 1) as follows. (i) The first method essentially is the traditional Hammett method [9] suitably modified by using the acidity function appropriate to the 'class' of bases under consideration. For each compound $\mathrm{p}K_{\mathrm{BH}^+}$ was obtained by plotting log *I* against H_o''' according to equation

$$\log C_{\mathrm{BH}^+}/C_{\mathrm{B}} = \log I = -mH_o''' + \mathrm{p}K_{\mathrm{BH}^+} \qquad (1)$$

(1), where C_{BH^+} and C_{B} are molar concentrations of conjugate acid and base respectively and H_o''' is the acidity function for tertiary aromatic amines.[10,11]



(I)

a; X = H
b; X = Br
c; X = CONH$_2$
d; X = CO$_2$Me
e; X = SO$_2$Me
f; X = Ac
g; X = CHO
h; X = CN
i; X = NO$_2$

The data reported in Table 1 show that the present bases closely follow the H_o''' acidity function with *m* values near unity. When *m* differs from unity $\mathrm{p}K_{\mathrm{BH}^+}$ values were calculated from H_o''' values at half-protonation $H_o'''_{(\frac{1}{2})}$, according to equation (2).

$$\mathrm{p}K_{\mathrm{BH}^+} = mH_o'''_{(\frac{1}{2})} \qquad (2)$$

(ii) The second, more general, method is to use the linear free energy relationship (3), originally proposed by Bunnett and Olsen.[12] Modena and Scorrano [13,14] have shown that,

$$\log I + H_o = \varphi(H_o + \log C_{\mathrm{H}^+}) + \mathrm{p}K_{\mathrm{BH}^+} \qquad (3)$$

provided that a plot of the left-hand side of equation (3) against $(H_o + \log C_{\mathrm{H}^+})$ is linear, thermodynamic $\mathrm{p}K_{\mathrm{BH}^+}$ values referred to infinite dilution in water as the standard state can be obtained for a wide range of bases of different structures. In fact Arnett and Scorrano [15] criticized the attempt of defining different acidity function scales for different 'classes' of bases [method (i) above] as 'each individual base defines its own acidity function', although 'experience has shown that φ values for compounds containing the same functional group lie in most cases in a narrow range'.[15]

From the values reported in Table 1 it appears that tertiary thiophen amines have φ values slightly lower than the parent tertiary anilines (φ from −0.33 to −0.48),[14,15] and this points to a smaller difference in solute–solvent interaction (activity coefficients) between the free base and its conjugate acid in the thiophen series. This is reasonable as the positive charge of the ammonium ion could well be more deeply buried in the more polarizable thiophen than the benzene moiety.

(iii) The third method is a recent version, developed by Yates and Cox,[16] of an earlier approach proposed by Marziano and Passerini.[17] These authors [16,17] still criticized the Bunnett–Olsen [12] approach [method (ii) above] because it also requires a Hammett-type acidity function, subject to an arbitrary assumption of cancellation of activity coefficient terms. This approach [16] involves the determination of 'excess acidity' values, *X*, for aqueous solutions of strong acids using a large number of bases of different structures. According to

Table 1. pK_{BH^+} Values of 5-substituted 3-nitro-2-*NN*-dimethylaminothiophens (I) and of 5-nitro-2-*NN*-dimethylaminothiophen

		H_0'''			Bunnett–Olsen			Yates–Cox		
Compound	$\lambda_{max.}$/nm	$-pK_{BH^+}$	m	r	$-pK_{BH^+}$	$-\varphi$	r	$-pK_{BH^+}$	m^*	r
(Ia)	430	1.69	1.00	0.999	1.60	0.68	0.994	1.56	1.60	0.996
(Ib)	435	3.02	1.02	0.995	2.91	0.65	0.978	2.92	1.50	0.994
(Ic)	415	4.32	0.93	0.998	4.21	0.39	0.990	4.25	1.25	0.997
(Id)	415	5.05	1.16	0.999	4.75	0.70	0.989	4.92	1.66	0.999
(Ie)	400	5.15	0.96	0.992	5.06	0.53	0.979	5.22	1.39	0.993
(Ih)	410	5.40	1.00	0.996	5.49	0.61	0.985	5.58	1.50	0.998
(Ii)	450	6.95	0.95	0.999	6.70	0.34	0.986	7.01	1.43	0.999
5-Nitro-2-*NN*-dimethylaminothiophen	450	1.70	0.57	0.997	1.57	−0.37	0.987	1.54	0.588	0.998

Table 2. Linear free energy relationships[a] for pK_{BH^+} values of 5-substituted 3-nitro-2-*NN*-dimethylaminothiophens

No.	Relationship	$\rho \pm s_\rho$	$i \pm s_i$	r	n
1	$(-pK_{BH^+})_A = \rho(\sigma^-)_P$	4.12 ± 0.24	0.08 ± 0.18	0.992	7
2	$(-pK_{BH^+})_A = \rho(\sigma^-)_P$	4.15 ± 0.06	−0.06 ± 0.05	1.000	5
3	$(-pK_{BH^+})_B = \rho(\sigma^-)_P$	4.07 ± 0.20	0.08 ± 0.15	0.994	7
4	$(-pK_{BH^+})_B = \rho(\sigma^-)_P$	4.10 ± 0.11	−0.03 ± 0.09	0.999	5
5	$(-pK_{BH^+})_C = \rho(\sigma^-)_P$	4.33 ± 0.19	0.06 ± 0.14	0.995	7
6	$(-pK_{BH^+})_C = \rho(\sigma^-)_P$	4.36 ± 0.08	−0.06 ± 0.07	0.999	5
7	$(-pK_{BH^+})_A = \rho(\sigma^-)_A$	3.80 ± 0.30	0.11 ± 0.25	0.984	7
8	$(-pK_{BH^+})_A = \rho(\sigma^-)_A$	3.85 ± 0.12	−0.09 ± 0.10	0.999	5
9	$(-pK_{BH^+})_B = \rho(\sigma^-)_A$	3.75 ± 0.27	0.11 ± 0.22	0.987	7
10	$(-pK_{BH^+})_B = \rho(\sigma^-)_A$	3.80 ± 0.19	−0.05 ± 0.17	0.996	5
11	$(-pK_{BH^+})_C = \rho(\sigma^-)_A$	3.99 ± 0.27	0.09 ± 0.22	0.989	7
12	$(-pK_{BH^+})_C = \rho(\sigma^-)_A$	4.04 ± 0.17	−0.08 ± 0.15	0.997	5

[a] ρ, Reaction constant; *i*, intercept of regression line with the ordinate; s_ρ and s_i, standard deviations of ρ and *i*, respectively; *r*, correlation coefficient; *n*, number of points. All the correlations are statistically significant at better then the 0.1% level. The values of pK_{BH^+} used in correlations are shown in Table 1. The subscripts A—C refer to H_0''', Bunnett–Olsen, and Yates–Cox methods, respectively. The substituent constants used in correlations are listed in Table 3.

this method[16] pK_{BH^+} values were determined as intercepts by plotting the left hand side of equation (4) against *X* values.[16]

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \qquad (4)$$

The slope, m^*, is characteristic of the protonation behaviour of the bases under consideration. The average value for this present series of bases (m^* 1.47 ± 0.22) is quite close to the value (m^* 1.65 ± 0.42) reported[16] for tertiary anilines. Inspection of Table 1 shows that the agreement among pK_{BH^+} values calculated by equations (1)—(4) is good and their thermodynamic significance is considered reliable at worst up to ±0.15 pK_{BH^+} units.

Discussion

The pK_{BH^+} values obtained by analysing the protonation data by the three different methods mentioned above correlate with the 'thiophen' σ^- values. The correlation is better with substituent constants obtained from piperidino-substitution reactions (ρ 4.1—4.3, *n* 7, *r* 0.992—0.995, see Table 2, lines 1, 3, and 5) than with those defined from anilinodebromination reactions (ρ 3.8—4.0, *n* 7, *r* 0.984—0.989, see Table 2, lines 7, 9, and 11). However, the validity of these substituent constants determined through the S_NAr studies is confirmed.

An examination of the plots obtained shows that in all the relationships the points for X = $CONH_2$ (Ic) and CO_2Me (Id) fall above the line as if these substituents had an effect higher than that expected: * this fact could be linked to partial protonation of these groups, which would make them more effective as electron withdrawers [this also pertains to compounds (If and g)]. It is well known that amides and esters can be protonated in strongly acidic media and the pK_{BH^+} values of these groups, estimated from literature data, are such as to render possible extensive protonation of the amide group,[18] and, probably, minor protonation of the ester group,[14,19] in the acidity ranges investigated.

All the calculated susceptibility constants (Table 2, lines 1—12) vary in the range expected for a reaction strongly affected by substituent electronic effects [minor variations are observed on exclusion of points referring to (Ic and d), compare any odd-numbered line of Table 2 with the following one].

The absolute values of susceptibility constants also deserve some comment in comparison with the situation for the benzene series. The 3- or 4-substituted *NN*-dimethylanilines[20a,c] have been extensively studied but only scanty data are available for 4-substituted 2-nitro-*NN*-dimethylanilines and 4-substituted 2,6-dinitro-*NN*-dimethylanilines.[20b,c,21] However, it is noteworthy that the three series of compounds give similar susceptibility constants (3.4, 3.1, and 3.4, respectively).

Thus our data for thiophens (I) indicate higher susceptibility constants in five-membered than in six-membered ring derivatives, as has been observed in some other instances.[1,2]

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* The plots obtained by excluding these two points give about the same susceptibility constants with higher correlation coefficients (*r* 0.999—1.000 or 0.996—0.999, respectively; see Table 2, lines 2, 4, 6, 8, 10, and 12).

Table 3. Substituent constants

Substituents	$(\sigma^-)_P$ [a]	$(\sigma^-)_A$ [b]
H	0.00	0.00
Br	0.35	0.40
$CONH_2$	0.55	0.58
CO_2Me	0.71	0.72
SO_2Me	0.85	0.95
Ac	0.85	0.89
CN	0.92	0.96
NO_2	1.27	1.38

[a] Values from ref. 3. [b] Values from ref. 4.

Some literature data concerning acidity constants of protonated 2-nitro- and 2,4-dinitro-*NN*-dimethylanilines [20a,c] allow comparison with the conjugate acids of the thiophen derivatives (Ia and i). Both thiophen compounds are stronger acids than their benzene counterparts (ΔpK_{BH^+} 4.4 and 6.0, respectively, have been calculated) and at least two factors contribute to this situation. First, the thienyl is more electron-withdrawing than the phenyl group; moreover the hyper-*ortho* [2,22] relation, characteristic of 2,3-disubstituted thiophens containing a strong electron-withdrawing and a strong electron-donating substituent, can determine in thiophens a strong resonance interaction between the *NN*-dimethylamino- and nitro-groups at variance with what happens in benzenes,[20a,c] where the steric hindrance between the two *ortho*-groups prevents this through-resonance.

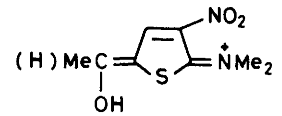
The predominance of this factor can be demonstrated by comparing *ortho-* and *para*-isomers in the thiophen and benzene series. 4-Nitro-*NN*-dimethylanilinium is a stronger acid than 2-nitro-*NN*-dimethylanilinium (ΔpK_{BH^+} *ca.* 2.0) indicating some difference between the *ortho-* and *para*-resonance interactions in the free bases, whereas 5-nitro- and 3-nitro-2-*NN*-dimethylaminothiophens (Ia) have about the same pK_{BH^+} values indicating similar *para*-like and hyper-*ortho*-interactions in thiophen compounds. An analogous role played by the hyper-*ortho* relation in thiophen derivatives has been pointed out in many instances by studies of reactivity [2] as well as of dynamic n.m.r. spectroscopy.[18]

Experimental

Materials.—Compounds (Ia—f, h—i) were prepared and purified according to the method reported.[23] Compound (Ig), m.p. 182—183 °C, was prepared according to ref. 23, purified by crystallization from ethanol–dioxan and gave satisfactory analytical data.

pK_{BH^+} *Measurements.*—Concentrated perchloric acid (Merck) was standardized against standard borax and/or sodium hydroxide. Acid solutions of appropriate concentrations were made up by diluting concentrated perchloric acid with twice distilled water. The absorbance of equivalent amounts of substrate in $HClO_4$ of various molarities was measured at appropriate [24] wavelengths, near $\lambda_{max.}$ of the base B (see Table 1). A reference cell containing acid of the same strength as that in the reaction cell was used in each case. The absorbance, *D*, was recorded immediately after the addition of substrate. Ionization ratios *I*, were calculated from equation (5) where D_B is the absorbance of the unprotonated substrate and D_{BH^+} that of its conjugate acid.

$$I = C_{BH^+}/C_B = (D_B - D)/(D - D_{BH^+}) \qquad (5)$$



(II)

A well known [25] difficulty arises in interpreting optical measurements in concentrated acid solutions, since the extinction coefficient of a given species may not be independent of composition. Special corrections must then be made to estimate how much of the absorbance change for B or BH^+ is due to conversion into its conjugate species and how much is due to a lateral medium shift of $\lambda_{max.}$.[15] In this present work we have adopted the simple graphical correction proposed by Johnson and Katritzky.[26] However, a more sophisticated method of multivariate analysis of the spectra,[27] to separate the effect of protonation from the medium effect, has recently been applied to thiophen-2-carboxamides,[18] a system related to ours. It appears [18] that the introduced corrections lie, in all but one case, well within the limits of reliability assumed for pK_{BH^+} of our substrates (see Results section).

In the case of compound (Ib) there is spectral evidence of a relatively slow decomposition of BH^+ (or B) at $HClO_4 \geqslant 6$M and formation of a product with $\lambda_{max.}$ 475 nm. Therefore for (Ib) we have studied the protonation only up to $HClO_4$ 5M (which corresponds to log *I* +0.292) and determined D_{BH^+} by extrapolating to zero time.

An analogous slow decomposition at $HClO_4 > 6$M has been observed for 5-nitro-2-*NN*-dimethylaminothiophen and the protonation followed only up to 6M-$HClO_4$ (which corresponds to log *I* +0.651).

We finally attempted to determine pK_{BH^+} for (If and g) and, in both cases, collected qualitative evidence of two overlapping protonation processes. The absorbance of (If) at 410 nm, corresponding to $\lambda_{max.}$ of B, first increases with increasing $HClO_4$ concentration in the range $0.5 \leqslant [HClO_4] \leqslant 6.5$M. The predominant species in $HClO_4$ 6.5M has $\lambda_{max.}$ 415 nm. A further increase of acid concentration shows a decrease in absorbance in the range $6.4 < [HClO_4] \leqslant 11.5$M with an estimated $H_o'''{}_{(+)} \simeq -7.2$ for the second protonation process. The protonation behaviour of (Ig) is strictly similar. We tentatively interpret these data as evidence of a preliminary protonation of the carbonyl group, the conjugate acid of which is stabilized by limiting structures such as (II). Subsequent protonation of the tertiary amino-group occurs only at very high acid concentration. It is noticeable that $H_o'''{}_{(+)}$ is in reasonable agreement with pK_{BH^+} expected from the substituent constant of the protonated acyl group.

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References

1 H. H. Jaffé and H. L. Jones, 'Advances in Heterocyclic Chemistry,' Academic Press, New York, 1964, vol. 3, p. 209; P. Tomasik and C. D. Johnson, *ibid.*, 1976, vol. 20, p. 1.

2 C. Dell'Erba and D. Spinelli, *Tetrahedron*, 1965, **21**, 1061; G. Guanti, C. Dell'Erba, and D. Spinelli, *J. Heterocycl. Chem.*, 1970, **7**, 1333; *J. Chem. Soc., Perkin Trans. 2*, 1972, 441; D. Spinelli, G. Consiglio, and A. Corrao, *ibid.*, p. 1866; D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *ibid.*, 1975, 620; G. Consiglio, D. Spinelli, S. Gronowitz, A.-B. Hörnfeldt, and R. Noto, *Chem. Scr.*, 1982, **19**, 46 and references therein.

3 D. Spinelli and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1975, 989.

4 G. Consiglio, C. Arnone, D. Spinelli, R. Noto, and V. Frenna, *J. Chem. Soc., Perkin Trans. 2*, 1981, 388.
5 H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.
6 A. Fischer, G. J. Leary, R. D. Topson, and J. Vaughan, *J. Chem. Soc. B*, 1966, 782.
7 H. Zollinger and C. Wittwer, *Helv. Chim. Acta*, 1955, **39**, 347; W. A. Sheppard, *J. Am. Chem. Soc.*, 1963, **85**, 1314.
8 H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, 1962, **84**, 3298.
9 C. H. Rochester, ' Acidity Functions,' Academic Press, London, 1970.
10 E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.*, 1964, **86**, 2671.
11 K. Yates, H. Wai, G. Welch, and R. A. McClelland, *J. Am. Chem. Soc.*, 1973, **95**, 418.
12 J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, 1966, **44**, 1899.
13 P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Am. Chem. Soc.*, 1973, **95**, 5960.
14 A. Levi, G. Modena, and G. Scorrano, *J. Am. Chem. Soc.*, 1974, **96**, 6585.
15 E. A. Arnett and G. Scorrano, *Adv. Phys. Org. Chem.*, 1976, **13**, 83.
16 R. A. Cox and K. Yates, *J. Am. Chem. Soc.*, 1978, **100**, 3861.
17 N. C. Marziano, G. M. Cimino, and R. Passerini, *J. Chem. Soc., Perkin Trans. 2*, 1975, 341.
18 G. Alberghina, M. E. Amato, S. Fisichella, and S. Occhipinti, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1722.
19 C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Am. Chem. Soc.*, 1968, **90**, 6492; V. Haldna, H. Kuura, T. Rodima, V. Timotheus, and E. Loodmaa, *Reakt. Sposobn. Org. Soedin.*, 1972, **9**, 427.
20 (*a*) K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, 1957, 1096; M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Am. Chem. Soc.*, 1959, **81**, 4226; E. M. Arnett and G. W. Mach, *ibid.*, 1966, **88**, 1177; (*b*) E. M. Arnett and G. W. Mach, *ibid.*, 1964, **86**, 2671; (*c*) J. L. Jensen and M. P. Gardner, *J. Phys. Chem.*, 1973, **77**, 1557.
21 K. Yates, H. Wai, G. Welch, and R. A. McClelland, *J. Am. Chem. Soc.*, 1973, **95**, 418.
22 D. Spinelli, R. Noto, and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1976, 747.
23 L. Lunazzi, D. Macciantelli, D. Spinelli, and G. Consiglio, *J. Org. Chem.*, 1982, **47**, 3759.
24 K. Yates, J. B. Stevens, and A. R. Katritzky, *Can. J. Chem.*, 1964, **42**, 1956.
25 R. P. Bell, ' The Proton in Chemistry,' Cornell Univ. Press, New York, 1959, p. 79.
26 C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and N. Shakin, *Tetrahedron*, 1965, **21**, 1055.
27 J. T. Edward and S. C. Wong, *J. Am. Chem. Soc.*, 1977, **99**, 4229.

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