PROTONATION OF SOME 5-SUBSTITUTED DI(2-THIENYL) KETONES IN SULFURIC ACID. A COMPARISON WITH OTHER 2-THIENYL AND PHENYL KETONES

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Dedicated to Professor Otto Exner on the occasion of his 75th birthday in recognition of his outstanding contributions to physical organic chemistry and chemometrics.

Protonation equilibria of some 5-substituted di(2-thienyl) ketones have been investigated spectrophotometrically in aqueous solutions of sulfuric acid at 298 K. The experimental pK_{BH^+} values have been analyzed by means of the Hammett equation. The calculated ρ as well as the pK_{BH^+} and m^* values have been compared with those for substituted 2-acetylthiophenes and phenyl 2-thienyl ketones.

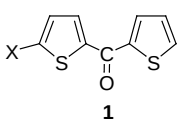
Key words: Acidity constants; Heterocyclic ketones; Linear free energy relationships; Thiophenes; Substituent effects; Hammett equation.

The study of the mechanisms of transmission of substituent effects through conjugate systems (vinyl, aryl, hetaryl) and of their influence on physical and chemical properties is one of the most important fields of physical organic chemistry. Thus, it appears relevant to know how a substituent, conjugated bridge (*e.g.* aromatic ring) and probe can interact as well as to understand the role of the single interacting "actors" (*e.g.*, the function of their structure and hence of their electronic and steric effects).

Among the studied probes, the carbonyl moiety has proven to be very rewarding. As a matter of fact ^{13}C and ^{17}O NMR chemical shifts[1], IR stretching frequencies[2], reactivities[3] as well as protonation equilibria[4] of aromatic carbonyl compounds have been widely investigated. The nature of the groups linked to the carbonyl carbon strongly affects both its electron density and conjugation ability. Thus, in ArCOY derivatives (Ar = aryl or

hetaryl) a shift has been observed from aldehydes[1e] and ketones[1e,5] (Y = H, R, Ar'), where the carbonyl exerts strong conjugative interactions with Ar, to amides [Y = NH_2 (refs[1e,6]), NHCl (ref.[7])], esters [Y = OR (refs[1e,5,6])] or acids [Y = OH (refs[1e,8])] characterized by a high degree of "internal" conjugation (*i.e.*, within the COY) and where the carbonyl thus essentially interacts with Ar through a π-polarization mechanism.

Within the framework of our interest in the transmission of substituent effects in aryl or hetaryl ketones, we have determined the protonation constants (pK_{BH^+}) of a series of 5-substituted di(2-thienyl) ketones **1** (Y = 2-thienyl). The results here thus complete the picture of substituent–heteroaromatic ring–probe interactions in the protonation of 2-thienylcarbonyl compounds, allowing a comparison with previous pK_{BH^+} data on 5-substituted 2-acetylthiophenes (Y = Me) **2** (ref.[9]) and phenyl 5-X-2-thienyl ketones (Y = C_6H_5) **3** (ref.[10]). An interesting facet is surely related to the possibility that in compounds **1**, the electronic interactions between the probe (*i.e.*, the carbonyl carbon) and the unsubstituted thiophene ring could affect those with the 5-substituted thiophene ring and *vice versa*. As a matter of fact, we pointed out that in the protonation reactions of phenylcarbonyl compounds on going from 4-substituted acetophenones (Y = Me) **4** (ref.[1f]), or benzophenones (Y = C_6H_5) **5** (ρ^+ value calculated from literature data[11]) to 4-X-phenyl 2-thienyl ketones (Y = 2-thienyl) **6** (ref.[10]) a lowering of the transmission of substituent effects (a sort of levelling or saturation effect) was observed: $\rho_4^+ \approx \rho_5^+ = 1.2$ and $\rho_6^+ = 1.0$, possibly due to the unsubstituted 2-thienyl moiety influencing the transmission of substituent effects from the 4-substituted benzene ring to the carbonyl carbon[10].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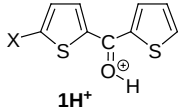
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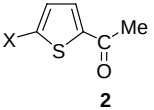
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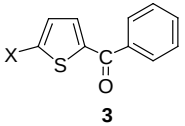
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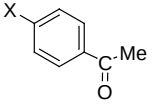
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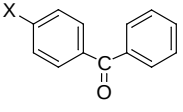
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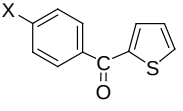
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Compounds **1** are weak organic bases which are protonated in concentrated solutions of strong acids. In this work the protonation equilibria of **1** have been studied in aqueous sulfuric acid at 298 K. Ionization values (*I* =

C_{BH^+}/C_B) have been determined spectrophotometrically and used to calculate the pK_{BH^+} values by means of the excess-acidity method[12] of Eq. (*1*),

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} , \qquad (1)$$

whose slope (m^*) usually allows to identify the nature of the base (*i.e.*, the site of protonation) and furnishes information about the degree of relative solvation of the conjugated acid-base pair[1f,12,13].

RESULTS AND DISCUSSION

The pK_{BH^+} and m^* values for the protonation equilibria of ketones **1** are collected in Table I.

The pK_{BH^+} value (–5.41) calculated for di(2-thienyl) ketone **1d** indicates that this compound is a weaker base than either 2-acetylthiophene[9] (pK_{BH^+} = –4.20) or phenyl 2-thienyl ketone[10] (pK_{BH^+} = –5.18). The relative basicities above seem to reflect the differences in the electronic effect that the methyl, phenyl and 2-thienyl groups can exert, as indicated by the acidity strengths of acetic acid (pK_a = 4.76), benzoic acid[14] (pK_a = 4.20) and

TABLE I
Protonation parameters for 5-X-2-thienyl 2-thienyl ketones **1**, determined by UV in aqueous sulfuric acid at 298 K

Substrate	X	$-K_{BH^+}$	m^*	r
1a	OMe	3.30 ± 0.06	0.88 ± 0.02	0.997
1b	SMe	3.75 ± 0.21	0.83 ± 0.06	0.990
1c	Me	4.53 ± 0.14	0.99 ± 0.04	0.992
1d	H	5.41 ± 0.08	1.08 ± 0.02	0.998
1e	Cl	5.67 ± 0.24	0.98 ± 0.05	0.986
1f	Br	5.70 ± 0.25	0.98 ± 0.02	0.984
1g	SOMe	6.40 ± 0.20	0.96 ± 0.04	0.989
1h	SO_2Me	7.10 ± 0.18	0.95 ± 0.08	0.982
1i	NO_2	7.19 ± 0.29	0.96 ± 0.04	0.990

thiophene-2-carboxylic acid[15] (pK_a = 3.51) and as the relevant σ_p values[16] ($\sigma_{p\text{-Me}}$ –0.17; $\sigma_{p\text{-}C_6H_5}$ –0.01; $\sigma_{p\text{-}\alpha C_4H_3S}$ 0.05) suggest.

Looking at 5-substituted di(2-thienyl) ketones **1**, a significant pK_{BH^+} variation (*ca* 4 units) was observed on going from the least basic (**1i**; X = NO_2) to the most basic compound (**1a**; X = OMe). The substituents affect the carbonyl basicity as expected: *i.e.*, electron-withdrawing and -donating substituents reduce and increase the basicity, respectively. The pK_{BH^+} values were analyzed by means of the Hammett equation, the best correlation (ρ^+ = 2.46 (± 0.06) σ^+ – 0.12 (± 0.03); S = 0.05, n = 9, r = 0.998) being obtained with the σ_p^+ set of substituent constants[16]. The ρ^+ value calculated for **1** is only slightly higher than those for compounds **2** and **3** (2.12 and 2.15, respectively[9,10]), although the conjugation between the carbonyl group and Y would be expected to cause here (where Y is a relatively highly conjugative 2-thienyl ring) an attenuation in the transmission of electronic effects from the substituted ring and hence a lower ρ value. A similar sensitivity of the transmission of substituent effects in **1** and **2** or **3** can be explained considering that for the substituents having a +M effect (OMe, SMe, Me, Cl and Br), a favourite conformation is that with the unsubstituted 2-thienyl ring turned out of the plane defined by the substituted ring and the carbonyl group. It is well known that the same conformation, with the phenyl group instead of the unsubstituted 2-thienyl ring, has been shown to be the preferred one for phenyl 2-thienyl ketones[17] **3**. The coplanarity between the carbonyl group and 2-thienyl ring having an electron-donor substituent is also supported by the use of the σ_p^+ set of substituent constants to indicate a direct interaction (extraconjugative interaction) between electron-donor substituents and probe. For electron-withdrawing substituents with a –M effect (SO_2Me and NO_2) and for SOMe, the greater ability of the unsubstituted 2-thienyl ring to conjugate with the carbonyl group makes more stable the conformation where such a ring and the carbonyl group are coplanar.

Semiempirical PM3 calculations confirm the hypothesis above for the base itself **1** though showing that the most probable conformation for the protonated **1H**$^+$ is that with both heterocyclic rings coplanar with the carbonyl group.

The replacement of the phenyl ring of **3** or of the methyl group of **2** with the 2-thienyl ring causes an increase in electron density on the carbonyl carbon[18], as confirmed by the relevant ^{13}C NMR chemical shifts in the unsubstituted **1** (180.49 ppm)[19], **2** (194.78 ppm)[20] and **3** (189.98 ppm)[21]. Thus, while electron-withdrawing substituents can presumably better exert their electron-attracting effect, electron-donating substituents should be

less able to increase the carbonyl carbon electron density in compounds **1** than in **2** or **3**; this can in turn explain similar ρ^+ values calculated for **1**, **2** and **3**. Such a similarity of susceptibility constants confirms indeed that in ketones **1**, **2** and **3** the nature of the second group bound to the carbonyl carbon (Me, Ar or Het) is a minor factor in determining their entity.

Since protonation equilibria of weak organic bases are strongly affected by both electronic (internal factors) and solvation effects (external factors), it is interesting to compare the influence of the latter on the protonation of **1** with respect to other aryl ketones.

For the 5-substituted di(2-thienyl) ketones **1**, *m** values ranging from 0.83 to 1.08 were calculated. Bearing in mind that *m** essentially evaluates the degree of relative solvation of the conjugated acid-base pair (**1H**$^+$–**1**), similar *m** values indicate that similar variations in the solute–solvent interactions occur in the series studied on going from the base to the conjugate acid. Furthermore, it must be emphasized that high values of *m**, such as 1.0, indicate that the protonation does not significantly increase the solvation with respect to the conjugate base. The mean value (0.96 ± 0.05) of *m** for compounds **1** is similar to that (0.85 ± 0.05) for 2-acetylthiophenes[9] **2** and much the same as that for phenyl 5-X-2-thienyl ketones[10] **3** (1.03 ± 0.07). These analogous *m** values seem to indicate that in 2-thienylcarbonyl compounds **1**, **2** or **3**, the relative solvation of the different conjugated acid-base pairs is not much sensitive to electronic and/or steric requirements of the Y group (2-thienyl, Me and Ph, respectively) as well as to the substituent on the hetaryl ring. On the contrary, for the three corresponding phenyl ketone series, *i.e.*, phenyl 2-thienyl ketones[10] **6**, acetophenones[1f] **4** and benzophenones[11] **5** (Y = 2-thienyl, Me and Ph, respectively), significant variations of *m** were observed (*m** = 0.97, 0.57 and 0.80, respectively). The overall *m** behaviour observed (constant for **1**, **2** and **3**, but variable for **4**, **5** and **6**) suggests that the 2-thienyl ring, owing to its high ability to conjugate with the carbonyl probe, exerts a levelling of solvation as a consequence of a kind of electronic effect saturation.

Finally, we can argue that the similar *m** values collected for **1**, **2** and **3** indicate that the differences in the pK_{BH^+} values observed for the above compounds must be essentially dependent on internal rather than on external factors. Moreover, the results obtained in the linear free energy pK_{BH^+} *vs* σ_p^+ relationship of compounds **1** confirm once again the larger aptitude of thiophene with respect to the benzene ring to transmit substituent electronic effects.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR 8300 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-E series 250 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard, coupling constants (*J*) are given in Hz. Flash chromatography was carried out using Macherey–Nagel silica gel (0.04–0.063 mm). Light petroleum refers to the fraction boiling at 40–60 °C.

Di(2-thienyl) ketone **1d** was purchased from Aldrich. Ketones **1c** (ref.[22]) and **1e** (ref.[23]) were obtained as reported. The same Friedel–Crafts procedure was used for the synthesis of the unknown bromo derivative **1f**, but it furnished very low yields of ketones **1a** and **1b**. Compound **1a** was then prepared from the bromo derivative by nucleophilic substitution with sodium methoxide in methanol in the presence of CuO.

The ketone **1b** was synthesized by a two-step procedure from 2-(methylsulfanyl)-thiophene, whose lithium derivative was allowed to react with thiophene-2-carbaldehyde to give [5-(methylsulfanyl)-2-thienyl](2-thienyl)methanol. By oxidation with pyridinium chlorochromate the latter gave the expected ketone in 36% overall yield.

Compounds **1g** (70%) and **1h** (50%) were obtained from **1b** by oxidation with sodium periodate and with hydrogen peroxide, respectively.

Several attempts were made in order to synthesize the nitro derivative **1i**. While the Friedel–Crafts reaction between thiophene and 5-nitrothiophene-2-carbonyl chloride did not take place, the nitration of **1b** gave an inseparable mixture of 4- and 5-nitrosubstituted di(2-thienyl) ketones. We eventually obtained **1i** by the reaction[24] of 5-nitrothiophene-2-carbonyl chloride with 2-(tributylstannyl)thiophene in the presence of a catalytic amount of Pd(II).

General Procedure for the Friedel–Crafts Synthesis of **1c**, **1e** and **1f**

Thiophene-2-carbonyl chloride (34.7 mmol) and $AlCl_3$ (38.0 mmol) were added portionwise to an ice-cooled solution of the 2-substituted thiophene (34.7 mmol) in CS_2 (50 ml). The reaction mixture was stirred for 30 min at 0 °C, then for 3 h at room temperature, and finally poured into ice-cool water and extracted with chloroform. The combined organic extracts were washed with brine and dried (Na_2SO_4); the solvent evaporation under reduced pressure gave a residue which was purified by chromatography.

5-Bromo-2-thienyl 2-thienyl ketone (**1f**): 64%; m.p. 70–71 °C. IR (DMSO solution): 1 618 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 7.17 d, 1 H, *J*(3,4) = 4.0 (H-3); 7.20 dd, 1 H, *J*(4',5') = 4.6, *J*(4',3') = 3.8 (H-4'); 7.66 d, 1 H, *J*(4,3) = 4.0 (H-4); 7.72 dd, 1 H, *J*(5',4') = 4.6, *J*(5',3') = 0.9 (H-5'); 7.88 dd 1 H, *J*(3',4') = 3.8, *J*(3',5') = 0.9 (H-3'). ^{13}C NMR (CD_3OD): 123.5, 129.5, 133.0, 134.9, 135.3, 135.7, 142.9, 145.7, 179.1. For $C_9H_5BrO_2S$ (257.1) calculated: 39.57% C, 1.84% H, 23.47% S; found: 39.80% C, 1.89% H, 23.30% S.

5-Methoxy-2-thienyl 2-thienyl ketone (**1a**): Sodium (131 mg, 5.70 mmol) was added to a suspension of **1f** (492 mg, 1.80 mmol) and CuO (71.6 mg, 0.9 mmol) in anhydrous methanol (5 ml). The reaction mixture was refluxed for 30 h. After cooling to room temperature, the suspension was filtered off and then water (15 ml) was added to the solution. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue obtained by concentration under reduced pressure was purified by chromatography (silica gel; light petroleum–ethyl acetate 15 : 1) recovering **1a** (182 mg,

45%); m.p. 49–50.5 °C. IR (DMSO solution): 1 607 cm^{-1} (C=O). ^1H NMR (CD_3OD): 4.00 s, 3 H (OCH_3); 6.43 d, 1 H, *J*(4,3) = 4.5 (H-4); 7.21 dd, 1 H, *J*(4',5') = 4.9, *J*(4',3') = 4.1 (H-4'); 7.77 d, 1 H, *J*(3,4) = 4.5 (H-3); 7.82 dd, 1 H, *J*(5',4') = 4.9, *J*(5',3') = 1.0 (H-5'); 7.88 dd, 1 H, *J*(3',4') = 4.1, *J*(3',5') = 1.0 (H-3'). ^{13}C NMR (CD_3OD): 61.2, 107.5, 129.2, 130.1, 133.8, 134.1, 136.3, 143.3, 176.5, 179.9. For $C_{10}H_8O_2S_2$ (224.3) calculated: 53.55% C, 3.60% H, 28.59% S; found: 53.74% C, 3.75% H, 28.40% S.

[5-(Methylsulfanyl)-2-thienyl](2-thienyl)methanol: Butyllithium (1.30 mol l^{-1} in hexane; 7.1 ml, 9.23 mmol) was added dropwise to a solution of 2-(methylsulfanyl)thiophene (1.00 g, 7.68 mmol) in anhydrous Et_2O (10 ml) at 0 °C under argon. After 30 min, thiophen-2-carbaldehyde (0.86 g, 7.68 mmol) was added *via* syringe and the mixture left standing at 0 °C for 10 min; then saturated aqueous NH_4Cl (15 ml) was added and the mixture allowed to warm to room temperature. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue obtained by concentration under reduced pressure was purified by chromatography (silica gel; light petroleum–ethyl acetate 25 : 1) giving the title compound as a red oil (1.21 g, 65%). IR (liquid film): 3 400 cm^{-1} (OH). ^1H NMR ($CDCl_3$): 2.40 s, 3 H (SCH_3); 2.62 d, 1 H, *J*(OH,H) = 3.1 (OH); 6.13 d, 1 H, *J*(H,OH) = 3.1 (C**H**OH); 6.76 d, 1 H, *J*(4,3) = 3.6 (H-4); 6.85 d, 1 H, *J*(3,4) = 3.6 (H-3); 6.90 dd, 1 H, *J*(4',5') = 5.1, *J*(4',3') = 3.6 (H-4'); 6.95 dd, 1 H, *J*(3',4') = 3.6, *J*(3',5') = 1.5 (H-3'); 7.22 dd, 1 H, *J*(5',4') = 5.1, *J*(5',3') = 1.5 (H-5'). For $C_{10}H_{10}OS_3$ (242.4) calculated: 49.56% C, 4.16% H, 39.68% S; found: 49.49% C, 4.22% H, 39.88% S.

5-(Methylsulfanyl)-2-thienyl 2-thienyl ketone (**1b**): [5-(Methylsulfanyl)-2-thienyl](2-thienyl)-methanol (288 mg, 1.19 mmol) in anhydrous dichloromethane (6 ml) was added *via* cannula to a suspension of pyridinium chlorochromate (530 mg, 2.39 mmol) in anhydrous dichloromethane (16 ml). The reaction mixture was stirred overnight at room temperature, then filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified by chromatography (silica gel; light petroleum–ethyl acetate 15 : 1) giving **1b** (160 mg, 56%); m.p. 68–69 °C. IR (DMSO solution): ν 1 606 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): 2.62 s, 3 H (SCH_3); 6.97 d, 1 H, *J*(4, 3) = 3.8 (H-4); 7.17 dd, 1 H, *J*(4',5') = 4.9, *J*(4',3') = 3.9 (H-4'); 7.67 dd, 1 H, *J*(5',4') = 4.9, *J*(5',3') = 0.8 (H-5'); 7.75 d, 1 H, *J*(3,4) = 3.8 (H-3); 7.85 dd, 1 H, *J*(3',4') = 3.9, *J*(3',5') = 0.8 (H-3'). ^{13}C NMR ($CDCl_3$): 19.5, 126.8, 127.9, 132.6, 133.1, 133.8, 141.9, 142.5, 150.1, 177.5. For $C_{10}H_8OS_3$ (240.4) calculated: 49.97% C, 3.35% H, 40.02% S; found: 50.12% C, 3.24% H, 39.89% S.

5-(Methylsulfinyl)-2-thienyl 2-thienyl ketone (**1g**): A solution of **1b** (1.00 g, 4.16 mmol) in methanol (15 ml) was added to a stirred solution of $NaIO_4$ (920 mg, 4.30 mmol) in water (8.6 ml) at 0 °C. The reaction mixture was stirred overnight at room temperature, then extracted with ethyl acetate and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue obtained by concentration under reduced pressure was purified by chromatography (silica gel; ethyl acetate) giving **1g** (747 mg, 70%); m.p. 95–96 °C. IR (DMSO solution): 1 622 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): 2.98 s, 3 H ($SOCH_3$); 7.23 dd, 1 H, *J*(4',5') = 4.8, *J*(4',3') = 3.7 (H-4'); 7.52 d, 1 H, *J*(4,3) = 4.0 (H-4); 7.77 dd, 1 H, *J*(5',4') = 4.8, *J*(5',3') = 1.0 (H-5'); 7.86 d, 1 H, *J*(3,4) = 4.0 (H-3); 7.92 dd, 1 H, *J*(3',4') = 3.7, *J*(3',5') = 1.0 (H-3'). ^{13}C NMR (CD_3OD): 44.7, 129.7, 130.3, 134.2, 135.6, 136.3, 143.0, 148.0, 156.2, 179.6. For $C_{10}H_8O_2S_3$ (256.4) calculated: 46.85% C, 3.15% H, 37.52% S; found: 47.04% C, 3.20% H, 37.70% S.

5-(Methylsulfonyl)-2-thienyl 2-thienyl ketone (**1h**): Hydrogen peroxide (30%, 0.57 ml) was added to a solution of **1b** (500 mg, 2.08 mmol) in acetic acid (4.2 ml). The reaction mixture was heated (70 °C) under stirring in a water bath for 45 min, then cooled and poured into

ice-water. The aqueous phase was then extracted with Et_2O and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue obtained by concentration under reduced pressure was purified by chromatography (silica gel; ethyl acetate) to give **1h** (283 mg, 50%); m.p. 130–131 °C. IR (DMSO solution): 1 626 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): 3.25 s, 3 H (SO_2CH_3); 7.23 dd, 1 H, *J*(4',5') = 5.00, *J*(4',3') = 3.40 (H-4'); 7.75 d, 1 H, *J*(4,3) = 3.95 (H-4); 7.80 dd, 1 H, *J*(5',4') = 5.00, *J*(5',3') = 0.8 (H-5'); 7.84 d, 1 H, *J*(3,4) = 3.95 (H-3); 7.92 dd, 1 H, *J*(3',4') = 3.40, *J*(3',5') = 0.8 (H-3'). ^{13}C NMR (CD_3OD): 45.7, 129.8, 133.8, 134.6, 136.0, 136.8, 142.9, 149.3, 150.1, 179.7. For $C_{10}H_8O_3S_3$ (272.4) calculated: 44.10% C, 2.96% H, 35.31% S; found: 44.32% C, 3.02% H, 35.07% S.

5-Nitro-2-thienyl 2-thienyl ketone (**1i**): 2-(Tributylstannyl)thiophene (95%, 1.85 g, 4.72 mmol) and *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (1.8 mg, $2.35 \cdot 10^{-3}$ mmol) were added to a solution of 5-nitrothiophene-2-carbonyl chloride (900 mg, 4.70 mmol) in HMPA (10 ml). The yellow solution was heated at 65 °C with stirring in a sealed tube for 1 h, then cooled to room temperature and diluted with water. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine and dried (Na_2SO_4). The residue obtained by concentration under reduced pressure was purified by chromatography (silica gel; light petroleum–Et_2O 4 : 1) to give **1i** (731 mg, 65%); m.p. 147 °C. IR (DMSO solution): 1 630 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): 7.25 dd, 1 H, *J*(4',5') = 4.9, *J*(4',3') = 3.9 (H-4'); 7.78 d, 1 H, *J*(4,3) = 4.3 (H-4); 7.83 dd, 1 H, *J*(5',4') = 4.9, *J*(5',3') = 1.0 (H-5'); 7.93 dd, 1 H, *J*(3',4') = 3.9, *J*(3',5') = 1.0 (H-3'); 7.92 d, 1 H, *J*(3,4) = 4.3 (H-3). ^{13}C NMR ($CDCl_3$): 127.9, 128.5, 130.6, 134.2, 135.4, 141.3, 147.0, 156.0, 177.8. For $C_9H_5NO_3S_2$ (239.3) calculated: 45.18% C, 2.11% H, 5.85% N, 26.80% S; found: 45.26% C, 2.19% H, 6.02% N, 26.52% S.

pK_{BH^+} *Measurements*. The pK_{BH^+} and *m** values reported in Table I are, respectively, the intercept and the slope (obtained by least-squares treatment) of the straight lines corresponding to Eq. (*1*) (ref.[12]). Ionization values ($I = C_{BH^+}/C_B$) were determined at 298.0 ± 0.5 K in aqueous sulfuric acid by spectroscopic UV techniques whose essential features have been previously described[1f]. The UV absorption spectra of solutions of **1** at different sulfuric acid concentrations were also affected by medium effects, thus no isosbestic point was detected. Medium effects on absorption curves were corrected by the characteristic vector analysis (CVA) method[25]. The absorption curves were reproduced at a 99% accuracy with only two vectors, the first, associated with the protonation process, accounting for about 95% of the total variability.

The C_{H^+} and *X* values used in Eq. (*1*) were calculated by interpolation of literature data[12].

Calculations. Semiempirical calculations and full geometry optimization were performed at the PM3 level of theory[26] by means of the MOPAC93 program available in the CS Chem3D ProTM package (version 3.5) for Macintosh, distributed by the Cambridge Soft Corporation.

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REFERENCES AND NOTES

1. a) St. Amour T. E., Burgar M. I., Valentine B., Fiat D.: *J. Am. Chem. Soc.* **1981**, *103*, 1128; b) Craik D. J., Brownlee R. T. C.: *Prog. Phys. Org. Chem.* **1983**, *14*, 1; c) Balakrishnan P., Baumstark A. L., Boykin D. W.: *Org. Magn. Reson.* **1984**, *22*, 753; d) Perunal S., Vasuki G., Wilson D. A.: *Magn. Reson. Chem.* **1990**, *28*, 257; e) Dahn H., Pechy P., Toan V. V.: *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 647; f) Chimichi S., Dell'Erba C., Gruttadauria M.,

Noto R., Novi M., Petrillo G., Sancassan F., Spinelli D.: *J. Chem. Soc., Perkin Trans. 2* **1995**, 1021.
2. a) Jones R. N., Forbes W. F., Mueller W. A.: *Can. J. Chem.* **1957**, *35*, 504; b) Laurence C., Berthelot M.: *J. Chem. Soc., Perkin Trans. 2* **1979**, 98; c) Helbert M., Berthelot M., Laurence C., Spinelli D., Consiglio G., Arnone C.: *Spectrochim. Acta, Part A* **1983**, *39*, 703.
3. a) Cox R. A., Smith C. R., Yates K.: *Can. J. Chem.* **1979**, *57*, 2952; b) Gal J. F., Geribaldi S., Pfister-Guillouzo G., Morris D. G.: *J. Chem. Soc., Perkin Trans. 2* **1985**, 103; c) Jones J. R., Pearson G. M., Spinelli D., Consiglio G., Arnone C.: *J. Chem. Soc., Perkin Trans. 2* **1985**, 557; d) Guthrie J. P., Cassar J., Klyn A.: *Can. J. Chem.* **1987**, *65*, 2154; e) De Maria P., Fontana A., Spinelli D.: *J. Chem. Soc., Perkin Trans. 2* **1991**, 1067; f) Murray R. W., Morgan M. M.: *J. Org. Chem.* **1991**, *56*, 684.
4. a) Stewart R.: *The Proton: Application to Organic Chemistry*. Academic Press, London 1985; b) Dell'Erba C., Mugnoli A., Noto R., Novi M., Occhiucci G., Petrillo G., Sancassan F., Spinelli D.: *Tetrahedron* **1997**, *53*, 731; and references therein.
5. Dell'Erba C., Sancassan F., Novi M., Petrillo G., Mugnoli A., Spinelli D., Consiglio G., Gatti P.: *J. Org. Chem.* **1988**, *53*, 3564.
6. Dell'Erba C., Mele A., Novi M., Petrillo G., Sancassan F., Spinelli D.: *J. Chem. Soc., Perkin Trans. 2* **1990**, 2055.
7. De Rosa M., Brown K., McCoy M., Ong K., Sanford K.: *J. Chem. Soc., Perkin Trans. 2* **1993**, 1787.
8. a) Noto R., Lamartina L., Arnone C., Spinelli D.: *J. Chem. Soc., Perkin Trans. 2* **1987**, 689; b) De Maria P., Fontana A., Spinelli D., Dell'Erba C., Novi M., Petrillo G., Sancassan F.: *J. Chem. Soc., Perkin Trans. 2* **1993**, 649.
9. Noto R., Gruttadauria M., Arnone C., Lamartina L., Spinelli D.: *J. Chem. Res., Synop.* **1993**, 274.
10. Noto R., Gruttadauria M., Rosselli S., Spinelli D.: *J. Chem. Soc., Perkin Trans. 2* **1996**, 829.
11. Bonner T., Phillips J.: *J. Chem. Soc. B* **1966**, 650.
12. Cox R. A., Yates K.: *J. Am. Chem. Soc.* **1978**, *100*, 3861.
13. Bagno A., Scorrano G., More O'Ferrall R. A.: *Rev. Chem. Intermed.* **1987**, *7*, 313.
14. Dean J. A.: *Handbook of Organic Chemistry*, Section 8-10. McGraw–Hill, New York 1987.
15. Spinelli D., Noto R., Consiglio G.: *J. Chem. Soc., Perkin Trans. 2* **1976**, 747.
16. Exner O.: *Correlation Analysis of Chemical Data*, p. 61. Plenum, New York–London 1988.
17. Scrowston R. M. in: *Thiophene and its Derivatives* (S. Gronowitz, Ed.), Part 3, p. 454. Wiley, New York 1986.
18. Several factors can contribute to such a result, *e.g.*, different hybridization (and hence electronegativity) of adjacent carbon atoms, the effect of the conformation around the carbonyl carbon, and variations of the anisotropic effects.
19. Noto R., Gruttadauria M., Spinelli D.: Unpublished data.
20. a) Noto R., Gruttadauria M., Rosselli S., Consiglio G., Spinelli D.: *J. Chem. Res., Miniprint* **1995**, 1382; b) Noto R., Gruttadauria M., Rosselli S., Consiglio G., Spinelli D.: *J. Chem. Res., Synop.* **1995**, 222.
21. Noto R., Gruttadauria M., Chimichi S., Petrillo G., Spinelli D.: *J. Phys. Org. Chem.* **1999**, *12*, 408.
22. Gol'dfarb Y. L., Konstantinov A.: *Bull. Acad. Sci. U.S.S.R., Div. Chem. Sci.* **1956**, 1013.
23. Buu-Hoi N. P., Hoŕn N., Xuong N. D.: *Rec. Trav. Chim. Pays-Bas* **1950**, *69*, 1083.
24. Stille J. K.: *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
25. Edward J. T., Wong S. C.: *J. Am. Chem. Soc.* **1977**, *99*, 1560.
26. a) Stewart J. J. P.: *J. Comput. Chem.* **1989**, *10*, 209; b) Stewart J. J. P.: *J. Comput. Chem.* **1989**, *10*, 221.