An Analysis of ^{13}C Nuclear Magnetic Resonance Substituent Chemical Shifts in 3-Substituted Thiophene-2-carboxylic and 2-Substituted Benzoic Acids by Linear Free Energy Relationships

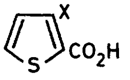
Renato Noto *
Istituto di Chimica Organica, Via Archirafi 20, Palermo 90123, Italia
Liliana Lamartina *
Dipartimento di Chimica e Tecnologie Farmaceutiche, Via Archirafi 32, Palermo 90123, Italia
Caterina Arnone and Domenico Spinelli
Dipartimento di Chimica Organica, Via S. Donato 15, Bologna 40127, Italia

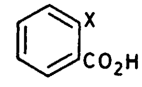
The ^{13}C n.m.r. chemical shifts of the title compounds and of the corresponding anions have been measured in methanol. The observed substituent chemical shifts have been analysed by means of cross-correlations and of single and dual substituent parameter linear free energy relationships. Different results have been obtained for thiophene and benzene derivatives using DSP analysis: for the first ring system the results have been rationalized in terms of separate resonance and inductive contributions of substituent effects (pointing out the occurrence of an apparent reverse polar effect); in contrast the same treatment of the data for the benzene system gave poor results, confirming once again the different proximity effects in six- and five-membered ring derivatives.

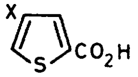
From studies of the reactivity of many classes of *ortho*-di-[1] or poly-substituted[2] thiophene derivatives and the application of linear free energy (l.f.e.) *ortho*-correlations to reactivity and equilibrium data, we have shown that in thiophene compounds it is possible to provide evidence for many examples of good l.f.e. *ortho*-correlations, both in reactions on the ring[1a—c] and on the side-chain,[1d—l] at variance with the results obtained for six-membered ring derivatives (*e.g.* benzene, naphthalene).[3]

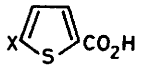
The aim of the present work is to ascertain whether an *ortho*-like substituent induces on the carbon of the side-chain in thiophene series a ^{13}C n.m.r. substituent chemical shift (SCS) which could give linear correlations by dual substituent parameter (DSP) treatment of data, duplicating the situation observed in reactivity and equilibrium studies. It must be noted that SCSs induced on side-chain carbon atoms in benzene derivatives by *ortho*-substituents are usually excluded from DSP treatment due to steric and/or magnetically anisotropic effects. We have chosen as probe compounds a series of 3-substituted thiophene-2-carboxylic acids (**1**)† and the corresponding anions (**1**$^-$), whose ^{13}C chemical shifts have been measured in deuteriated methanol.

In order to enable a comparison between the effects of *ortho*-substituents in thiophene- and benzene-carboxylic acids we have also collected ^{13}C n.m.r. data of *ortho*-substituted benzoic acids (**2**) and the corresponding anions (**2**$^-$) under similar experimental conditions.


(1)


(2)


(3)


(4)

a; X = NO_2
b; X = SO_2Me
c; X = SOMe
d; X = Ac
e; X = I
f; X = F
g; X = Br
h; X = H
i; X = SMe
j; X = Me
k; X = OMe

Recently,[4] we measured the ^{13}C n.m.r. chemical shifts of some 4- (**3**) and 5-substituted (**4**) thiophene-2-carboxylic acids and of the corresponding anions (**3**$^-$) and (**4**$^-$) in deuteriated methanol and analysed the induced SCSs by both single (Hammett) and DSP l.f.e. relationships, the latter being generally more successful. We used the 'unconstrained' version (1)‡ of the DSP equation developed by Ehrenson *et al.*[5]

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R + i \qquad (1)$$

This equation separates substituent effects into polar (σ_I) and resonance (σ_R) components and uses one of the four different resonance scales [σ_R^+, σ_R^-, σ_R^{BA}, and σ_R^0] depending on the electronic demand at the reaction or measuring site. We have chosen for the DSP analysis a series of substituents whose σ_I and σ_R constant sets are orthogonal to each other (depending on the substituent scales used the *r*-values range from 0.01 to 0.23).

Results and Discussion

The SCSs induced on the ring carbon atoms are collected in Tables 1 and 2. In Tables 3 and 4 the SCSs induced on the carboxylic carbon atom (C-α) are reported together with the pK_a values of the corresponding carboxylic acids.

Owing to the superimposition of resonance, field, and anisotropy effects[6] the attempts to correlate SCSs of endocyclic carbon atoms, by using both Hammett and DSP equations, usually give poor results. In our case only the SCSs of the C-2 (*ortho*-conjugated) carbon atom in both (**1**) and (**1**$^-$) showed statistically significant correlations. The values of the susceptibility constants ρ_I and ρ_R calculated using σ_R^{BA} [ρ_I

---

† *Note added in proof.* Recently, H. Satonara, K. Abe, and M. Hirata (*Bull. Chem. Soc. Jpn.*, 1987, **60**, 391) have reported a ^{13}C n.m.r. study and MNDO calculations of some 5-, 4-, and 3-(substituted methyl)thiophene-2-carboxylates. The SCS of ring carbons of the esters in $CDCl_3$ are linearly correlated with those of the corresponding carbons of 2- and 3-substituted thiophenes, showing good fits for *para*- and *meta*-like esters and poor fits for *ortho*-like esters. We have observed that SCS of all the esters studied by Satonara *et al.* give good linear correlations with SCS of the corresponding acids and anions (*r* 0.94—0.99).

‡ Concerning the use of equation (1) see ref. 4.

Table 1. SCS values of ring carbon atoms of 3-X-thiophene-2-carboxylic acids (**1**) and anions (**1**$^-$) in CD_3OD[a]

Compound	X	C-2	C-3	C-4	C-5	Others[c]
(**1b**)	SO_2Me	1.70	10.54	2.39	−2.29	43.88
(**1c**)	SOMe	−4.76	18.24	−2.60	0.16	42.90
(**1d**)	Ac	1.22	11.17	1.65	−0.95	201.80, 30.53
(**1e**)	I	−2.94	−47.69	11.13	0.52	
(**1f**)[b]	F	−21.49	27.05	−9.44	−1.91	
(**1g**)	Br	−6.16	−16.96	5.26	−0.82	
(**1h**)[c]	H	135.69	134.58	128.89	133.82	
(**1i**)	SMe	−12.71	12.64	−1.72	−1.19	16.32
(**1j**)	Me	−7.02	12.56	3.97	−2.46	15.93
(**1k**)	OMe	−25.03	29.17	−11.29	−1.38	59.44
(**1b**$^-$)	SO_2Me	4.86	8.83	1.77	−2.57	*d*
(**1c**$^-$)	SOMe	−2.84	16.17	−2.92	0.09	43.45
(**1d**$^-$)	Ac	2.81	11.41	0.29	−3.39	201.21, 30.02[e]
(**1e**$^-$)	I	−2.29	−49.55	10.53	0.41	
(**1f**$^-$)[f]	F	−22.52	27.51	−9.08	−2.74	
(**1g**$^-$)	Br	−5.87	−18.83	4.98	−1.21	
(**1h**$^-$)[c]	H	144.76	130.79	128.01	129.87	
(**1i**$^-$)	SMe	−11.13	9.11	−1.32	−1.30	16.49
(**1j**$^-$)	Me	−6.78	10.47	4.14	−2.99	15.70
(**1k**$^-$)	OMe	−24.35	28.10	−10.34	−2.45	59.26

[a] ^{13}C chemical shifts (in p.p.m.) relative to the unsubstituted compound (**1h**) or (**1h**$^-$). Downfield shifts are positive. [b] $^2J_{C\text{-}2,F}$ 10.4, $^1J_{C\text{-}3,F}$ 274.2, $^2J_{C\text{-}4,F}$ 25.6, $^3J_{C\text{-}5,F}$ 10.3, and $^3J_{C\text{-}\alpha,F}$ 3.5 Hz. [c] Chemical shifts (in p.p.m.) relative to Me_4Si. [d] Signal not detected due to deuterium exchange or overlapping by solvent peaks. [e] Value of deuterium-substituted methyl. [f] $^2J_{C\text{-}2,F}$ 10.5, $^1J_{C\text{-}3,F}$ 265.1, $^2J_{C\text{-}4,F}$ 27.5, $^3J_{C\text{-}5,F}$ 10.9, and $^3J_{C\text{-}\alpha,F}$ 3.3 Hz.

Table 2. SCS values of ring carbon atoms of 2-X-benzoic acids (**2**) and of the corresponding anions (**2**$^-$) in CD_3OD[a]

Compound	X	C-1	C-2	C-3	C-4	C-5	C-6	Others[c]
(**2a**)	NO_2	−2.94	19.54	−4.62	−0.80	4.39	0.41	
(**2b**)	SO_2Me	3.61	9.54	1.37	−1.80	5.51	0.09	45.21
(**2c**)	SOMe	−3.00	19.50	−4.77	1.05	2.40	1.73	44.40
(**2e**)	I	6.01	−36.66	12.90	−0.57	−0.38	0.84	
(**2f**)[b]	F	−11.45	32.76	−11.55	1.75	−4.24	2.56	
(**2g**)	Br	2.79	−8.75	5.83	−0.48	−1.00	1.34	
(**2h**)[c]	H	132.01	130.73	129.45	134.01	129.45	130.73	
(**2i**)	SMe	−3.09	13.75	−3.61	−0.41	−4.89	1.74	15.64
(**2j**)	Me	−0.42	10.31	3.19	−1.05	−2.69	0.94	21.74
(**2k**)	OMe	−10.87	29.78	−15.92	1.17	−7.79	2.20	56.67
(**2a**$^-$)	NO_2	−0.82	17.96	−4.25	−1.65	5.44	−0.54	
(**2b**$^-$)	SO_2Me	4.81	7.26	0.86	−2.20	6.08	−0.83	*d*
(**2c**$^-$)	SOMe	−2.33	17.78	−4.95	0.91	2.53	1.40	45.34
(**2d**$^-$)	Ac	2.84	9.92	0.91	−1.19	2.50	−2.97	207.27, 29.94[e]
(**2e**$^-$)	I	9.72	−37.71	11.70	−1.26	0.02	−1.74	
(**2f**$^-$)[f]	F	−9.98	31.53	−11.82	0.48	−4.04	1.39	
(**2g**$^-$)	Br	5.44	−10.72	5.03	−1.27	−0.62	−1.11	
(**2h**$^-$)[c]	H	139.35	130.25	128.66	131.11	128.66	130.25	
(**2i**$^-$)	SMe	0.82	8.73	−2.41	−1.03	−3.76	−0.56	16.16
(**2j**$^-$)	Me	3.01	5.61	2.48	−2.23	−2.53	−2.08	20.53
(**2k**$^-$)	OMe	−7.34	27.56	−15.87	−0.72	−7.45	−0.56	56.21

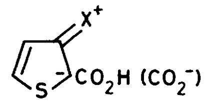
[a] ^{13}C chemical shifts (in p.p.m.) relative to the unsubstituted compound (**2h**) or (**2h**$^-$). Downfield shifts are positive. [b] $^2J_{C\text{-}1,F}$ 10.3, $^1J_{C\text{-}2,F}$ 258.2, $^2J_{C\text{-}3,F}$ 22.5, $^3J_{C\text{-}4,F}$ 9.0, $^4J_{C\text{-}5,F}$ 3.9, $^3J_{C\text{-}6,F}$ 0.9, and $^3J_{C\text{-}\alpha,F}$ 3.2 Hz. [c] Chemicals shifts (in p.p.m.) relative to Me_4Si. [d] Signal not detected due to deuterium exchange or overlapping by solvent peaks. [e] Value of deuterium-substituted methyl. [f] $^2J_{C\text{-}1,F}$ 14.8, $^1J_{C\text{-}2,F}$ 248.6, $^2J_{C\text{-}3,F}$ 23.2, $^3J_{C\text{-}4,F}$ 8.3, $^4J_{C\text{-}5,F}$ 3.7, $^3J_{C\text{-}6,F}$ 3.6, and $^3J_{C\text{-}\alpha,F}$ 1.6 Hz.

-1.9 ± 4.7 and ρ_R 36 ± 4 (r 0.960) for (**1**) and ρ_I 0 ± 5 and ρ_R 39 ± 4 (r 0.962) for (**1**$^-$)] point out that the variation in the electron density at the C-2 carbon atom depends only on the mesomeric effect of substituents.

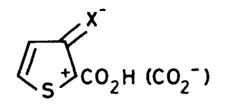
The goodness of fit in the Hammett equation and other similar approaches involving l.f.e. relationships depends upon the used parameters. Generally these parameters are useful for correlation analysis, but the errors inherent in the determination of these 'constants' and the uncertainty in the kind of 'constants' to be used would also recommend the use of the direct comparison between the various measurements in addition to such a correlation.

For this reason we have attempted to correlate the SCSs relative to endocyclic carbon atoms of (**1**) or (**2**) with the SCSs of the corresponding anions (**1**$^-$) or (**2**$^-$). Because of their relative smallness, which bears no apparent relation to polar and resonance effects, the SCSs induced on *meta* endocyclic carbon atoms gave poor results in cross-correlations (see lines 4, 9, and 11 of Table 5).

In contrast excellent correlations for both thiophene and benzene carboxylic acids were obtained in all the other instances (see lines 1—3, 6—8, and 10 of Table 5). The occurrence of the above cross-correlations and the slope values close to unity indicate that the interactions between the carboxylic or the carboxylate group and the present substituent are of the same kind and of a similar extent, in spite of the different electronic effects exerted by carboxylic or carboxylate groups (*e.g.* compare substituent constants $\sigma_{p\text{-COOH}}$ 0.45 and $\sigma_{p\text{-COO}^-}$ 0.00).[7] This observation agrees with the hypothesis that electronic interactions occur essentially between the X-substituent and the aromatic ring and do not involve the carboxylic (or carboxylate) group, as sketched in (**5**) and (**6**).



(**5**)



(**6**)

Table 3. SCS values of carboxylic carbon atoms of the 3-X-thiophene-2-carboxylic acids and of the corresponding anions (1^-) in CD_3OD[a]

X	SCS(1)	SCS(1^-)	$-\Delta pK_a$[b]
SO_2Me	−3.02	−4.01	0.95
SOMe	−1.90	−2.91	0.59
Ac	−1.52	−0.77	0.55
I	−1.55	−1.86	0.25
F	−1.91	−2.39	0.40
Br	−1.75	−2.07	0.27
H[c]	165.34	170.34	
SMe	−0.08	0.10	−0.35
Me	0.68	1.18	−0.39
OMe	−0.30	−0.23	−0.74

[a] ^{13}C chemical shifts (in p.p.m.) relative to the unsubstituted compound (**1h**) or (**1h**$^-$). Downfield shifts are positive. [b] D. Spinelli, R. Noto, and G. Consiglio, *J. Chem. Soc., Perkin Trans. 2*, 1976, 747. [c] Chemical shifts (in p.p.m.) relative to Me_4Si.

Table 4. SCS values of carboxylic carbon atoms of the 2-X-benzoic acids (**2**) and of the corresponding anions (2^-) in CD_3OD[a]

X	SCS(2)	SCS(2^-)	$-\Delta pK_a$[b]
NO_2	−1.74	−1.87	0.71
SO_2Me	0.33	−0.28	0.64
SOMe	−1.63	−3.29	0.52
Ac	*c*	0.15	0.36
I	0.23	1.52	0.34
F	−2.42	−2.51	0.34
Br	−0.28	0.38	0.37
H[d]	169.91	175.71	
SMe	−0.06	0.72	0.14
Me	1.36	3.21	−0.06
OMe	−0.35	0.91	0.10

[a] ^{13}C chemical shifts (in p.p.m.) relative to the unsubstituted compound (**2h**) or (**2h**$^-$). Downfield shifts are positive. [b] J. F. J. Dippy, *Chem. Rev.*, 1939, **25**, 151; M. Hojo, M. Utaka, and Z. Yoshida, *Tetrahedron*, 1971, **27**, 4031. [c] See Spectroscopic Measurements in the Experimental section. [d] Chemical shifts (in p.p.m.) relative to Me_4Si.

Interestingly, different results were obtained in the correlation of SCSs of carboxylic carbon atoms; thiophenecarboxylic acids gave an acceptable result (*r* 0.967, line 5 of Table 5) whereas benzoic acids gave a poor result (*r* 0.909, line 12 of Table 5). This confirms once again the difference in l.f.e. correlations between six- and five-membered ring derivatives.[1]

We have also attempted a correlation of the SCSs of thiophene endocyclic carbon atoms *versus* the SCSs of the corresponding benzene carbon atoms, in order to test if the same substituent effects affect the endocyclic carbon atoms of the two aromatic rings. The results reported in Table 6 show that only the SCSs of the thiophene C-3 and C-4 can be described by the SCSs of benzene C-2 and C-3, respectively (see lines 2—3 and 13—14 of Table 6). The slope of the cross-correlation for thiophene C-4 and benzene C-3 is meaningfully lower than unity (*s* 0.80) according to the different double-bond character of the C(3)–C(4) bond in the thiophene ring (hypo-*ortho* relation)[1a,i,k,8] compared with the aromatic C(2)–C(3) bond in the benzene ring.

We have also carried out a correlation of the SCSs of endocyclic carbon atoms of compounds (**1**) and (1^-) *vs.* those of 4-substituted thiophene-2-carboxylic acids (**3**) and anions (3^-),[4] respectively. Good correlations (*r ca.* 0.98) have been observed for *ortho*-conjugated and *ipso* endocyclic carbon atoms (see lines 6—7 and 17—18 of Table 6). As expected, *meta* endocyclic carbon atoms did not furnish significant correlations (see lines 9 and 20 of Table 6). Concerning the *ortho*-unconjugated carbon atoms [C-4 in (**1**) and C-3 in (**3**)] the SCSs seem to be affected by the different conformation that the substituent and the carboxylic group can assume in acids (**3**). Consequently, in this case, we obtained statistically poor correlations ($0.94 > r > 0.91$, see lines 8 and 19 of Table 6).

Data in Tables 3 and 4 show that *ortho*-substituents cause small variations ($\leqslant 4$ p.p.m.) of ^{13}C chemical shifts of the carboxy carbon atom. However, different situations are observed for thiophene and benzene derivatives. In fact in the thiophene series [compounds (**1**) and (1^-)] the observed SCSs are systematic depending on electronic effects and show the so-called *reverse* substituent effect;[9] *i.e.* electron-withdrawing sub-

Table 5. Statistical data[a] for the correlations between SCSs of anions (1^-) and (2^-) *vs.* those of the corresponding acids (**1**) and (**2**)

Line	Series	^{13}C site	$s \pm s_s$	$i \pm s_i$	*n*	*r*	*f*
1	(1^-)	C-2	1.06 ± 0.04	1.38 ± 0.46	10	0.995	0.09
2	(1^-)	C-3	1.01 ± 0.02	−1.41 ± 0.42	10	0.999	0.06
3	(1^-)	C-4	0.94 ± 0.03	−0.13 ± 0.17	10	0.997	0.08
4	(1^-)	C-5	1.18 ± 0.25	−0.40 ± 0.35	10	0.860	0.38
5	(1^-)	C-α	1.36 ± 0.13	0.24 ± 0.20	10	0.967	0.22
6	(2^-)	C-1	1.00 ± 0.09	2.27 ± 0.49	10	0.972	0.27
7	(2^-)	C-2	0.98 ± 0.03	−2.04 ± 0.56	10	0.997	0.08
8	(2^-)	C-3	0.95 ± 0.02	−0.28 ± 0.19	10	0.998	0.07
9	(2^-)	C-4	0.84 ± 0.17	−0.80 ± 0.18	10	0.868	0.40
10	(2^-)	C-5	1.01 ± 0.03	0.46 ± 0.12	10	0.996	0.09
11	(2^-)	C-6	0.58 ± 0.42	−1.16 ± 0.60	10	0.446	0.67
12	(2^-)	C-α	1.57 ± 0.25	−0.59 ± 0.30	10	0.909	0.51

[a] *s*, slope of the regression line; *i*, intercept; s_s and s_i, standard deviations; *n*, number of points; *r*, correlation coefficient; *f*, goodness of the fit.

Table 6. Statistical data[a] for the correlations between SCSs of 3-substituted derivatives [(**1**) or (**1**$^-$)] *vs.* those of related benzene derivatives [(**2**) or (**2**$^-$)] or of 4- [(**3**) or (**3**$^-$)] or 5-substituted [(**4**) or (**4**$^-$)] derivatives

Line	Series	^{13}C site in (**1**)—(**1**$^-$)	$s \pm s_s$	^{13}C site in (**2**)—(**4**) or (**2**$^-$)—(**4**$^-$)	$i \pm s_i$	n	r	f
1	SCS(**1**)	C-2	(1.37 ± 0.26)SCS(**2**)	C-1	-6.22 ± 1.55	9	0.894	0.38
2	SCS(**1**)	C-3	(1.13 ± 0.06)SCS(**2**)	C-2	-3.73 ± 1.39	9	0.989	0.17
3	SCS(**1**)	C-4	(0.80 ± 0.03)SCS(**2**)	C-3	0.86 ± 0.22	9	0.996	0.10
4	SCS(**1**)	C-5	(0.20 ± 0.35)SCS(**2**)	C-4	-1.03 ± 0.38	9	0.214	1.07
5	SCS(**1**)	C-α	(0.49 ± 0.37)SCS(**2**)	C-α	-0.94 ± 0.40	9	0.449	0.98
6	SCS(**1**)	C-2	(0.84 ± 0.07)SCS(**3**)	C-5	-3.26 ± 0.95	8	0.978	0.18
7	SCS(**1**)	C-3	(0.91 ± 0.07)SCS(**3**)	C-4	0.41 ± 1.32	8	0.982	0.17
8	SCS(**1**)	C-4	(1.10 ± 0.17)SCS(**3**)	C-3	1.18 ± 0.93	8	0.934	0.43
9	SCS(**1**)	C-5	(0.00 ± 0.19)SCS(**3**)	C-2	-1.37 ± 0.33	8	0.002	2.08
10	SCS(**1**)	C-α	(1.86 ± 0.22)SCS(**3**)	C-α	0.32 ± 0.21	8	0.959	0.21
11	SCS(**1**)	C-α	(1.29 ± 0.32)SCS(**4**)	C-α	-0.04 ± 0.33	8	0.856	0.44
12	SCS(**1**$^-$)	C-2	(1.27 ± 0.38)SCS(**2**$^-$)	C-1	-7.70 ± 2.17	10	0.763	0.69
13	SCS(**1**$^-$)	C-3	(1.16 ± 0.07)SCS(**2**$^-$)	C-2	-2.61 ± 1.38	10	0.985	0.19
14	SCS(**1**$^-$)	C-4	(0.78 ± 0.04)SCS(**2**$^-$)	C-3	0.90 ± 0.29	10	0.991	0.15
15	SCS(**1**$^-$)	C-5	(0.90 ± 0.39)SCS(**2**$^-$)	C-4	-0.61 ± 0.51	10	0.632	0.68
16	SCS(**1**$^-$)	C-α	(0.56 ± 0.23)SCS(**2**$^-$)	C-α	-1.34 ± 0.40	10	0.655	1.08
17	SCS(**1**$^-$)	C-2	(0.82 ± 0.08)SCS(**3**$^-$)	C-5	-3.31 ± 1.08	7	0.978	0.17
18	SCS(**1**$^-$)	C-3	(0.93 ± 0.05)SCS(**3**$^-$)	C-4	-0.97 ± 0.96	8	0.991	0.13
19	SCS(**1**$^-$)	C-4	(1.04 ± 0.19)SCS(**3**$^-$)	C-3	1.35 ± 1.00	8	0.912	0.51
20	SCS(**1**$^-$)	C-5	(0.37 ± 0.26)SCS(**3**$^-$)	C-2	-1.96 ± 0.47	8	0.494	0.87
21	SCS(**1**$^-$)	C-α	(1.62 ± 0.25)SCS(**3**$^-$)	C-α	0.72 ± 0.35	8	0.935	0.30
22	SCS(**1**$^-$)	C-α	(1.28 ± 0.29)SCS(**4**$^-$)	C-α	0.30 ± 0.41	8	0.876	0.42

[a] *s*, slope of the regression line; *i*, intercept; *n*, number of points; s_s and s_i, standard deviations; *r*, correlation coefficient; [f] goodness of the fit.

Table 7. L.f.e. relationships of induced SCSs for carboxylic carbon atoms of acids (**1**) and (**2**), or anions (**1**$^-$) and (**2**$^-$)

Line	Series	$s \pm s_s$	$i \pm s_i$	n	r	f
1	SCS(**1**)	$-(1.94 \pm 0.37)(-\Delta pK_a)$	-0.84 ± 0.19	10	0.888	0.39
2	SCS(**2**)	$-(2.29 \pm 1.30)(-\Delta pK_a)$	0.25 ± 0.52	10	0.530	1.39
3	SCS(**1**$^-$)	$-(2.57 \pm 0.60)(-\Delta pK_a)$	-0.90 ± 0.31	10	0.833	0.52
4	SCS(**2**$^-$)	$-(4.83 \pm 1.89)(-\Delta pK_a)$	1.42 ± 0.74	11	0.649	1.42
5	SCS(**1**)	$-(5.05 \pm 0.70)\sigma_I$	0.46 ± 0.26	10	0.930	0.29
6	SCS(**2**)	$-(3.11 \pm 1.31)\sigma_I$	0.64 ± 0.55	10	0.642	1.12
7	SCS(**1**$^-$)	$-(7.13 \pm 0.95)\sigma_I$	0.96 ± 0.35	10	0.936	0.31
8	SCS(**2**$^-$)	$-(5.63 \pm 2.04)\sigma_I$	1.85 ± 0.83	11	0.677	1.19
9	SCS(**1**)	$-(3.03 \pm 0.70)\sigma_p$	-0.61 ± 0.24	10	0.836	0.46
10	SCS(**2**)	$-(1.13 \pm 1.05)\sigma_p$	-0.23 ± 0.42	10	0.355	1.89
11	SCS(**1**$^-$)	$-(3.94 \pm 1.14)\sigma_p$	-0.61 ± 0.39	10	0.774	0.62
12	SCS(**2**$^-$)	$-(2.87 \pm 1.49)\sigma_p$	0.56 ± 0.60	11	0.541	1.71

[a] *s*, slope of the regression line; *i*, intercept; *n*, number of points; s_s and s_i standard deviations; *r*, correlation coefficient; *f*, goodness of the fit.

stituents cause upfield shifts of the carboxy resonance, the methyl group induces downfield shifts, and both methylthio and methoxy groups have practically no effect (<0.3 p.p.m.). In contrast in the benzene series the SCS values of the C-α carbon atom are not easily related to the electronic effects of the substituent, reflecting the influence of steric and/or other effects involving a direct structural interaction between the substituent and the carboxylic group.

We have made some attempts to correlate the SCSs of the C-α carbon atom of the thiophene derivatives (**1**) and (**1**$^-$) either with the ΔpK_a values of acids (**1**) or with some substituent constants (σ_I or σ_p). The obtained results were unsatisfactory (Table 7). This is consistent with the ^{13}C chemical shifts and pK_a or Hammett substituent constant values being related to different electronic densities, *e.g.* chemical shifts depend on the π-electron density on the carboxy carbon atom while both pK_a values and substituent constants such as σ_p depend on the total electron density of the carboxy group. It must be noted that similar results were obtained by us when studying 5-substituted thiophene-2-carboxylic acids (**4**).[4] Only the correlations of the SCSs for acids (**1**) and anions (**1**$^-$) with σ_I gave acceptable results (see lines 5 and 7 of Table 7; $r \geqslant 0.93$) showing that electronic effects are predominantly inductive in nature (see below).

In order to ascertain whether the same substituent effects operate on the C-α of the isomeric thiophene-2-carboxylic acids and anions, we attempted a correlation of the SCSs of *ortho*-substituted acids (**1**) with those of *meta* (**3**) or *para* (**4**) substituted acids (see lines 10—11 and 21—22 of Table 6), obtaining better results with (**3**) than with (**4**).

The analysis of C-α SCSs for (**1**) and (**1**$^-$) according to equation (1) has allowed us to calculate separate susceptibility constants (Table 8) for resonance and polar effects; the best fits were obtained with σ_R^{BA} values.* Correlations relative to the benzoic acids (**2**) and anions (**2**$^-$) gave statistically meaningless results (see lines 3—4 of Table 8: $r < 0.7$). In contrast, data for

---

* Also in the case of acids (**3**) and (**4**) and of anions (**3**$^-$) and (**4**$^-$) the best fit in DSP analysis was obtained using σ_R^{BA} values.[4]

Table 8. DSP analysis[a] of SCS data for the carboxylic carbon atoms according to equation (1) and using σ_R^{BA}

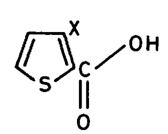
Line	Series	$\rho_I \pm s_{\rho}^{I}$	$\rho_R \pm s_{\rho}^{R}$	$i \pm s_i$	n	r	f
1	SCS(**1**)	-5.04 ± 0.41	-1.43 ± 0.35	0.23 ± 0.16	10	0.980	0.17
2	SCS(**1**$^-$)	-7.11 ± 0.74	-1.56 ± 0.63	0.71 ± 0.30	10	0.966	0.24
3	SCS(**2**)	-3.39 ± 1.36	1.20 ± 1.30	0.93 ± 0.64	10	0.690	1.08
4	SCS(**2**$^-$)	-3.44 ± 1.42	0.77 ± 0.88	0.98 ± 0.64	11	0.683	1.94
5	SCS(**3**)[b]	-2.81 ± 0.15	-0.74 ± 0.13	-0.03 ± 0.05	10	0.994	0.08
6	SCS(**3**$^-$)[b]	-4.11 ± 0.24	-1.10 ± 0.21	-0.09 ± 0.08	10	0.993	0.10
7	SCS(**4**)[b]	-2.86 ± 0.31	0.42 ± 0.40	0.02 ± 0.13	10	0.961	0.19
8	SCS(**4**$^-$)[b]	-4.23 ± 0.24	-1.16 ± 0.33	-0.10 ± 0.10	9	0.992	0.09

[a] ρ_I, ρ_R, susceptibility constants; i, intercept; s_ρ and s_i, standard deviations; n, number of points; r, correlation coefficent; f, goodness of the fit. [b] R. Noto, L. Lamartina, C. Arnone, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1987, 689.

the thiophene carboxylic acids (**1**) and anions (**1**$^-$) gave good correlations (see lines 1—2 of Table 8: $r > 0.96$) and this agrees with our previous data on the different role played by the proximity effects in the two aromatic rings.[1]

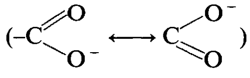
The susceptibility constants calculated for the C-α of thiophene carboxylic acids show that the polar component predominates ($|\rho_I| > |\rho_R|$), whereas the negative sign of ρ_I values represents a reverse SCS effect indicating that the polar component of the carboxy carbon chemical shift is almost exclusively controlled by π-polarization of the CO π-electrons induced by the dipole of the substituent. Moreover, as previously observed in the *meta* and *para* series,[4] the ρ_I (absolute value) observed for anions (**1**$^-$) is higher than that of the acids (**1**) in accord with the greater polarizability of the carboxylate carbon atom with respect to carbon atom of the undissociated carboxy group. As a matter of fact the sign (negative) of the ρ_R values confirms that the canonical structures determined by the conjugative interactions between the substituent and the carboxy group through the π-aromatic system are not relevant.

The correlations found point out that the proximity effects are absent or not so large as to affect l.f.e. correlations in the thiophene series; moreover the occurrence of a l.f.e. correlation indicates that the carboxylic group assumes the same conformation in all the studied compounds. The negative sign of ρ_I (reverse SCS effect) in the correlations involving acids (**1**) agrees with an *s-trans* conformation which has been proposed for other compounds containing a carbonyl group at C-2 in the thiophene ring.[10] Now, we have found that the *s-trans* conformation (**7**) is the preferred one in acids (**1**) irrespectively of the size of the substituent in the *ortho* position.



(7)

Finally, a comparison of DSP treatment results for the series *meta*, *para*, and *ortho* shows that in the anions the ρ_R values are roughly constant so indicating that the internal conjugation



$(-C(=O)O^- \longleftrightarrow C(O^-)=O)$ is able to interrupt the conjugation with the substituted ring.

In the *ortho* acids (**1**) and anions (**1**$^-$) the ρ_I values are higher than those for the corresponding *meta* and *para* series.[4] If the polar effects are essentially electric field effects, the ρ_I values measured for (**1**) and (**1**$^-$) depend on the distance between the substituent and the carboxylic (or carboxylate) group which is shorter in the *ortho* than in the *meta* and *para* derivatives. It must be noted that in the various series of acids and anions the field effects are transmitted through different media; in *ortho*-substituted acids through the solvent and in both *meta* and *para* derivatives through the molecular core. Therefore, microscopic dielectric constants are different and consequently the increase of ρ_I is not dependent only on substituent–carboxylic group distance values.

The different blend of inductive and mesomeric contributions peculiar for each series of acids [(**1**), (**3**), and (**4**)] and anions [(**1**$^-$), (**3**$^-$), and (**4**$^-$)] justify the statistical results obtained when the SCSs of C-α of the *ortho* derivatives are correlated with those of the *meta* and *para* derivatives (see above).

Conclusions

A comparison of the ^{13}C n.m.r. chemical shifts of 3-substituted thiophene-2-carboxylic acids with those of 2-substituted benzoic acids revealed a difference in the substituent influence on the variation of electron density at carbon sites of the two aromatic rings.

In thiophene carboxylic acids and anions [(**1**) and (**1**$^-$)] the SCSs of the C-α carbon atom show that the transmission of substituent effects along the side-chain occurs through the apparent reverse polar effect arising from a reverse polarization of electronic density at this site. Good fits were obtained when these data were treated by the DSP equation. Both the reverse polar effect and the negative sign of ρ_I suggest an *s-trans* conformation for the carboxylic group in all the compounds (**1**) studied.

In contrast, DSP analysis of SCSs of benzoic acids and anions [(**2**) and (**2**$^-$)] gave poor results, once again confirming the difference in proximity effects in six- and five-membered ring derivatives.

Experimental

Spectroscopic Measurements.—^{13}C N.m.r. spectra of acids (**1**) and (**2**) and anions (**1**$^-$) and (**2**$^-$) were run as previously reported.[4] In particular, in thiophene derivatives peaks assignment was based on substituent chemical shift considerations, with the aid of proton coupled spectra. In benzene derivatives, the assignment of the ring carbon atoms was made by observing induced SCSs by subsequent additions of small amounts of sodium methoxide to a solution of the acid; in a few cases an alternative assignment was possible, then we ascribed SCS values in such a way as to obtain better correlations.

The 2-acetylbenzoic acid (**2d**) in solution was in fast equilibrium with the cyclic form, according to literature spectroscopic data;[11] so for this compound the chemical shifts measured (omitted in Tables 2 and 4) were the average of the values relative to both forms.

Synthesis and Purification of Compounds.—The substituted benzoic acids (**2a**, **d**—**h**, **j**, **k**) were commercial samples purified by crystallization. 2-Methylthio- (**2i**),[3b] 2-methylsulphinyl- (**2c**),[12] 2-methylsulphonyl- (**2b**)[12] benzoic acids, and 3-acetylthiophene-2-carboxylic acid (**1d**)[13] were prepared according to literature methods. The other substituted thiophene-2-carboxylic acids were prepared as previously described.[14]

Acknowledgements

We thank the C.N.R. and Ministero P.I. for support.

References

1 (*a*) D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Chem. Soc., Perkin Trans. 2*, 1972, 441; (*b*) D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *ibid.*, 1975, 620; (*c*) D. Spinelli, G. Consiglio, and R. Noto, *ibid.*, 1976, 1495; (*d*) D. Spinelli, R. Noto, and G. Consiglio, *ibid.*, 1976, 747; (*e*) D. Spinelli, R. Noto, G. Consiglio, and A. Storace, *ibid.*, 1976, 1805; (*f*) G. Consiglio, S. Gronowitz, A.-B. Hörnfeldt, R. Noto, K. Petterson, and D. Spinelli, *Chem. Scr.*, 1978—79, **13**, 20; (*g*) G. Consiglio, S. Gronowitz, A.-B. Hörnfeldt, R. Noto, and D. Spinelli, *ibid.*, 1980, **15**, 49; (*h*) G. Consiglio, D. Spinelli, S. Fisichella, G. Alberghina, and R. Noto, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1153; (*i*) G. Consiglio, S. Gronowitz, A.-B. Hörnfeldt, R. Noto, and D. Spinelli, *Chem. Scr.*, 1980, **16**, 117; (*j*) R. Noto, S. Buscemi, G. Consiglio, and D. Spinelli, *J. Heterocycl. Chem.*, 1981, **18**, 735; (*k*) G. Consiglio, S. Gronowitz, A.-B. Hörnfeldt, and D. Spinelli, *Chem. Scr.*, 1982, **19**, 46; (*l*) G. Consiglio, D. Spinelli, S. Gronowitz, A.-B. Hörnfeldt, and R. Noto, *ibid.*, 1984, **23**, 116.

2 D. Spinelli, G. Consiglio, and A. Corrao, *J. Chem. Soc., Perkin Trans. 2*, 1972, 1866.

3 (*a*) J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1934, 161; J. F. J. Dippy, *Chem. Rev.*, 1939, **25**, 151; G. Kortum, W. Vogel, and K. Andrussow, *Pure Appl. Chem.*, 1961, **1**, 190; J. H. Elliot and M. Kilpatrick, *J. Phys. Chem.*, 1941, **45**, 454, 472, and 485; J. F. J. Dippy, S. R. C. Hughes, and B. C. Kitchener, *J. Chem. Soc.*, 1964, 1275; N. B. Chapman, J. Shorter, and J. H. P. Utley, *ibid.*, 1963, 1291; E. Tommila, J. Paasivirta, and K. Setala, *Suom. Kem.*, 1960, **33B**, 187; M. Hojo, M. Utaka, and Z. Yoshida, *Kogyo Kagaku Zassi*, 1965, **23**, 1034 and 1040; D. P. Evans, J. J. Gordon, and H. B. Waston, *J. Chem. Soc.*, 1937, 1430; A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brieux, *J. Chem. Soc. B*, 1966, 963; N. E. Sbarbati, *J. Org. Chem.*, 1965, **30**, 3365; (*b*) M. Hojo, M. Utaka, and Z. Yoshida, *Tetrahedron*, 1971, **27**, 4031.

4 R. Noto, L. Lamartina, C. Arnone, and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1987, 689.

5 S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, 1973, **10**, 1.

6 J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972, pp. 106—112.

7 D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 240.

8 S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, *Chem. Scr.*, 1975, **7**, 76.

9 W. F. Reynolds, *Prog. Phys. Org. Chem.*, 1983, **14**, 165.

10 R. Roques, S. Combrisson, C. Riche, and C. Pascard-Billy, *Tetrahedron*, 1970, **26**, 3555; H. J. Streurman and H. Schenk, *Recl. Trav. Chim. Pays-Bas.*, 1970, **89**, 392; L. Kafer and T. J. De Boer, *ibid.*, 1970, **89**, 825; A. Arcoria, S. Fisichella, and D. Sciotto, *Tetrahedron Lett.*, 1973, 2907.

11 P. R. Jones and P. J. Desio, *J. Org. Chem.*, 1965, **30**, 4293.

12 F. Arndt, F. Kirsch, and P. Nachtwey, *Ber. Dtsch. Chem. Ges.*, 1926, **59**, 1074.

13 M. Robba, B. Roques, and M. Bonhomme, *Bull. Soc. Chim. Fr.*, 1967, 2495.

14 S. Fisichella, S. Occhipinti, G. Consiglio, D. Spinelli, and R. Noto, *Phosphorus Sulfur*, 1982, **13**, 59.

Received 29th June 1987; *Paper* 7/1161