An Analysis of ^{13}C Nuclear Magnetic Resonance Substituent Chemical Shifts in 4- and 5-Substituted Thiophene-2-carboxylic Acids by Linear Free Energy Relationships

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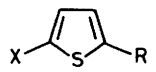
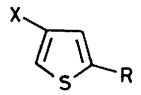
The ^{13}C n.m.r. chemical shifts of some 4- and 5-substituted thiophene-2-carboxylic acids and of the corresponding anions have been measured in methanol. The observed substituent chemical shifts have been compared with the calculated values and then analysed according to single and dual substituent parameter linear free energy relationships. The results have been rationalized in terms of separate resonance and inductive contributions of substituent effects. The resonance term has shown that no conjugation occurs between the ring and the carboxy group.

From a study of the variation of ^{13}C n.m.r. chemical shifts in a series of substituted aromatic compounds information[1] can be obtained on the transmission of substituent effects. The analysis of data usually is carried out by using both single and dual substituent parameter (DSP) linear free energy relationships (l.f.e.r.s), the latter generally being more successful.[1] Moreover n.m.r. data have been correlated[2] with i.r., reactivity, or equilibrium data but the results obtained have not always been satisfactory. This indicates that the mechanisms which control substituent effects on ^{13}C n.m.r. chemical shifts are rather different from those observed by other spectroscopic techniques (*e.g.*, i.r.) or by reactivity studies.

Continuing our researches[3] in the field of the transmission of the substituent effects in the thiophene ring, which we have thoroughly investigated by applying the classical '*meta*' and '*para*' and the less usual '*ortho*' l.f.e.r.s to kinetic and equilibrium constant measurements, we now report a ^{13}C n.m.r. spectroscopic study in deuteriated methanol of some 5- [(**1**), '*para*'-like] and 4-substituted* [(**3**), '*meta*'-like] thiophene-2-carboxylic acids and of the corresponding anions (**2**) and (**4**), respectively.



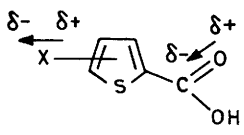
(**1**), (**2**), (**5**)



(**3**), (**4**), (**6**)

in (**1**) and (**3**) R = CO_2H
in (**2**) and (**4**) R = CO_2^-
in (**5**) and (**6**) R = H

a; X = NO_2 **e**; X = Br **l**; X = SMe
b; X = SO_2Me **f**; X = Cl **m**; X = Me
c; X = CO_2H **g**; X = I **n**; X = Pr^i
d; X = Ac **h**; X = F **o**; X = OMe
i; X = H



(**7**)

Our attention has been particularly focused on the substituent chemical shift (SCS) induced on the carboxylic carbon atom.

Literature data provide ^{13}C n.m.r. chemical shifts in deuteriated acetone for 2- (**5**) and 3-substituted (**6**) thiophenes as well as an analysis of substituent effects on ^{13}C chemical shifts of the ring carbon atoms.[4] Moreover some 4(2)-methylthiophene-2(4)-carboxylic acid derivatives have been examined[5] in deuteriated DMSO. Finally the influence of the thiophene ring on the ^{13}C chemical shifts of side-chain carbon atoms has also been studied for some series of substituted thiophenes.[6]

Results and Discussion

The SCSs induced on the ring carbon atoms are collected in Tables 1 and 2. We report the shifts calculated on the basis of the additivity of substituent effects in parentheses.[4] Tables 3 and 4 report the SCSs induced on the carboxylic carbon atom (C-α) together with the pK_a values of the corresponding carboxylic acids.

The SCS values obtained can be correlated by both single (Hammett) and DSP equations. In recent years, among the various two-parameter equations used to calculate separately the transmission coefficients for resonance and polar effects the DSP equation (1) developed by Ehrenson *et al.*[7] to analyse ^{13}C

$$SCS = \rho_I\sigma_I + \rho_R\rho_R \quad (1)$$

n.m.r. chemical shifts has been much used. This equation uses one of the four different resonance scales σ_R^+, σ_R^-, $\sigma_{(BA)}$, or σ_R^0,[7] depending on the electronic demand.

Some attempts to correlate SCS values, relative to endocyclic carbons, by using both single and DSP† [Table A of Supplementary Publication No. SUP 56669 (3 pp.)‡] equations, gave

* The substituents chosen for the DSP correlations show σ_I and σ_R constant sets which are orthogonal to each other (depending on the substituents used the r values range from 0.02 to 0.22).

† As a matter of fact we have used the 'unconstrained' version (2) of the

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R + i \quad (2)$$

Taft equation which allows one to estimate the standard deviations of the regression parameters. However, the results obtained by the two equations were not significantly different.

‡ Details of Supplementary Publications are in *J. Chem. Soc., Perkin Trans.* 2, 1987, Issue 1.

Table 1. SCS values of ring carbon atoms of 5-X-thiophene-2-carboxylic acids (**1**) and of the corresponding anions (**2**) in CD_3OD[a]

Compound	X	C-2	C-3	C-4	C-5
(**1a**)	NO_2	6.36 (9.1)	−1.92 (1.1)	0.76 (2.6)	22.43 (25.6)
(**1b**)	SO_2Me	7.36	−0.44	5.55	14.77
(**1c**)	CO_2H	5.91 (7.9)	−0.49 (1.3)	5.20 (7.0)	7.78 (9.1)
(**1d**)	Ac	6.75 (8.8)	−0.62 (1.6)	5.74 (6.2)	16.14 (19.8)
(**1e**)	Br	1.63 (2.5)	0.37 (1.2)	3.61 (3.4)	−13.04 (−13.6)
(**1f**)	Cl	−0.88 (−0.3)	−0.37 (−0.4)	−0.05 (0.1)	3.98 (4.1)
(**1g**)	I	5.93 (6.9)	1.08 (2.4)	10.39 (10.3)	−49.79 (−52.0)
(**1i**)	H[b]	135.69	134.58	128.89	133.82
(**1l**)	SMe	−0.52 (3.0)	0.59 (0.8)	0.32 (4.2)	15.12 (12.0)
(**1m**)	Me	−2.61 (−1.9)	0.54 (0.2)	−1.28 (−1.4)	15.75 (14.2)
(**1o**)	OMe	−15.16 (−13.2)	0.04 (−1.8)	−22.28 (−23.1)	40.29 (41.8)
(**2a**)	NO_2	7.25 (9.1)	−1.40 (1.1)	1.03 (2.6)	23.89 (25.6)
(**2b**)	SO_2Me	8.91	−0.56	6.27	14.60
(**2d**)	Ac	8.32 (8.8)	0.24 (1.6)	6.25 (6.2)	16.79 (19.8)
(**2e**)	Br	2.05 (2.5)	0.40 (1.2)	3.52 (3.4)	−13.54 (−13.6)
(**2f**)	Cl	−0.82 (−0.3)	−0.72 (−0.4)	−0.20 (0.1)	3.69 (4.1)
(**2g**)	I	6.38 (6.9)	1.03 (2.4)	10.47 (10.3)	−53.02 (−52.0)
(**2i**)	H[b]	144.76	130.79	128.01	129.87
(**2l**)	SMe	1.10 (3.0)	−0.10 (0.8)	3.03 (4.2)	13.01 (12.0)
(**2m**)	Me	−2.57 (−1.9)	0.32 (0.2)	−1.48 (−1.4)	15.03 (14.2)
(**2o**)	OMe	−14.85 (−13.2)	−1.08 (−1.8)	−22.57 (−23.1)	40.82 (41.8)

[a] ^{13}C Chemical shifts (in p.p.m.) relative to the unsubstituted compound (**1i**) or (**2i**). Downfield shifts are positive. In parentheses are reported the values calculated from ref. 4. [b] Chemical shifts (in p.p.m.) relative to Me_4Si.

Table 2. SCS values of ring carbon atoms of 4-X-thiophene-2-carboxylic acids (**3**) and of the corresponding anions (**4**) in CD_3OD[a]

Compound	X	C-2	C-3	C-4	C-5
(**3a**)	NO_2	1.64 (3.3)	−6.64 (−4.2)	20.48 (22.5)	0.25 (3.6)
(**3b**)	SO_2Me	3.35	−2.75	14.36	4.62
(**3d**)	Ac	1.43 (1.9)	−1.30 (0.2)	14.98 (16.4)	5.89 (7.9)
(**3e**)	Br	1.96 (1.9)	1.48 (2.9)	−17.73 (−17.3)	−2.77 (−2.2)
(**3h**)	F	−1.19 (0.8)	−11.52 (−9.5)	29.77 (31.9)	−21.63 (−21.4)
(**3i**)	H[b]	135.69	134.58	128.89	133.82
(**3l**)	SMe	1.33 (1.5)	0.21 (1.1)	7.59 (7.8)	−6.15 (−6.3)
(**3m**)	Me	−0.46 (0.5)	1.83 (2.8)	10.97 (10.9)	−4.31 (−4.3)
(**3n**)	Pr^i	−0.36	−0.49	23.15	−6.56
(**3o**)	OMe	−1.75 (0.0)	−9.27 (−7.4)	30.82 (32.5)	−27.53 (−28.3)
(**4a**)	NO_2	1.96 (3.3)	−6.70 (−4.2)	20.80 (22.5)	1.27 (3.6)
(**4b**)	SO_2Me	3.97	−3.02	13.81	*c*
(**4d**)	Ac	1.72 (1.9)	−1.33 (0.2)	15.41 (16.4)	7.21 (7.9)
(**4e**)	Br	1.35 (1.9)	1.89 (2.9)	−18.03 (−17.3)	−2.37 (−2.2)
(**4h**)	F	−1.09 (0.8)	−11.16 (−9.5)	30.21 (31.9)	−21.94 (−21.4)
(**4i**)	H[b]	144.76	130.79	128.01	129.87
(**4l**)	SMe	0.87 (1.5)	0.72 (1.1)	7.34 (7.8)	−5.20 (−6.3)
(**4m**)	Me	−0.41 (0.5)	2.07 (2.8)	10.77 (10.9)	−4.39 (−4.3)
(**4n**)	Pr^i	−0.35	−0.24	23.10	−6.77
(**4o**)	OMe	−1.70 (0.0)	−8.67 (−7.4)	31.15 (32.5)	−27.55 (−28.3)

[a] ^{13}C Chemical shifts (in p.p.m.) relative to the unsubstituted compound (**3i**) or (**4i**). Downfield shifts are positive. In parentheses are reported the values calculated from ref. 4. [b] Chemical shifts (in p.p.m.) relative to Me_4Si. [c] Deuterium substituted C-5 signal is not observed.

generally poor results on account of combined resonance, field, and anisotropy effects.[8] Indeed, only the SCS values of the C-2 ('*para*' conjugated) carbon in the 5-substituted and those of the C-5 ('*ortho*' conjugated) carbon in the 4-substituted thiophene-2-carboxylic acids and in the corresponding anions gave statistically significant correlations ($r > 0.95$;* for comments on these DSP analyses see below). Similar results have been found by Gronowitz and his co-workers[4] for 2- and 3-substituted thiophenes. They observed significant correlations (r 0.99 and 0.97, respectively), by using the DSP (Swain–Lupton) equation,[9] for the SCS values relative to the '*para*' conjugated carbon atom in 2-substituted and to the '*ortho*' conjugated carbon atom in 3-substituted thiophenes.

We found chemical shifts different (generally 1—2 p.p.m., see Tables 1 and 2) from those calculated on the basis of the corresponding shifts of monosubstituted thiophenes.[4] Apart from any consideration of the additivity principle it must be remarked that some difference was expected because our data and those on monosubstituted thiophenes have been determined in different solvents, methanol and acetone, respectively. Good linear correlations with slopes close to unity are obtained

* The SCS values of the iodo-substituted compounds have been excluded from the correlations, owing to the large anisotropy effect of the iodine substituent. Moreover the data relative to methylthio-substituted derivatives have been excluded from the calculation, because no reliable σ_R^+ is reported in the literature for the methylthio substituent.[7]

Table 3. SCS values of carboxylic carbon atoms of the 5-X-thiophene-2-carboxylic acids and of the corresponding anions in CD_3OD[a]

X	SCS(1)	SCS(2)	SCS(1) − SCS(2)	$-\Delta pK_a$[b]
NO_2	−1.70	−3.11	1.41	0.73
SO_2Me	−1.67	−2.61	0.94	0.70
CO_2H	−0.56			0.46[c]
Ac	−0.83	−1.58	0.75	0.51
Br	−1.37	−1.69	0.32	0.24
Cl	−1.14	−1.57	0.43	0.21
I	−1.56	−1.77	0.21	0.14
H[d]	165.34	170.34		
SMe	−0.68	−0.84	0.16	0.00
Me	0.12	0.23	−0.11	−0.23
OMe	0.42	0.45	−0.03	−0.27

[a] ^{13}C Chemical shifts (in p.p.m.) relative to the unsubstituted compound (**1i**) or (**2i**). Downfield shifts are positive. [b] Ref. 10. [c] D. Spinelli, R. Noto, and G. Consiglio, unpublished results. [d] Chemical shifts (in p.p.m.) relative to Me_4Si.

Table 4. SCS values of carboxylic carbon atoms of the 4-X-thiophene-2-carboxylic acids and of the corresponding anions in CD_3OD[a]

X	SCS(3)	SCS(4)	SCS(3) − SCS(4)	$-\Delta pK_a$[b]
NO_2	−2.02	−2.93	0.91	0.71[c]
SO_2Me	−1.74	−2.63	0.89	0.61
Ac	−0.86	−1.33	0.47	0.36
Br	−1.24	−1.96	0.72	0.36[c]
F	−1.06	−1.52	0.46	0.36
H[d]	165.34	170.34		
SMe	−0.61	−0.87	0.26	0.23
Me	0.12	0.13	−0.01	−0.07[c]
Pr^i	0.19	0.20	−0.01	−0.11
OMe	−0.24	−0.43	0.19	0.10

[a] ^{13}C Chemical shifts (in p.p.m.) relative to the unsubstituted compound (**3i**) or (**4i**). Downfield shifts are positive. [b] D. Spinelli, R. Noto, and G. Consiglio, unpublished results. [c] Ref. 10. [d] Chemical shifts (in p.p.m.) relative to Me_4Si.

between our data and those of monosubstituted thiophenes (Table 5) for ^{13}C chemical shifts of carbon atoms '*ortho*' or '*para*' to the variable substituent, indicating that mutual substituent interactions are not large. Because of the relatively small SCSs induced on '*meta*' endocyclic carbons atoms, the statistical treatments gave very poor results (not reported) for this site. The absence of large electronic interactions between the carboxylic group and the present substituent agrees with some of our previous results.[10] In fact, the pK_a values of a series of 4- and 5-substituted thiophene-2-carboxylic acids gave a good Hammett l.f.e.r. (ρ 0.98, *r* 0.998, *n* 13) by using the σ_m and σ_p substituent constants.*

In contrast, when such functional groups as OH, O^-,[11] or other groups[12] able to conjugate are present, in *para*-substituted derivatives substituent–substituent interactions play an important role on account of the large extra-conjugation. For example, when the SCS values of C-1 in *para*-substituted phenoxides[11] were plotted against the corresponding values in monosubstituted benzenes, large deviations from linearity were observed. Better results were obtained if electron-releasing and -withdrawing groups were separated in two linear correlations.

The SCS values reported in Tables 3 and 4 show that '*meta*' and '*para*' substituents have a relatively small influence on the ^{13}C chemical shifts of the side-chain carboxy carbon atom.

Table 5. Statistical data[a] for the correlations between induced SCSs of ring carbon atoms of acids (**1**) and (**3**) or anions (**2**) and (**4**) and those of related thiophenes

Compounds	^{13}C site	$s + s_s$	$i + s_i$	*n*	*r*	*f*
(**1**)	C-2	0.96 ± 0.06	−1.45 ± 0.38	10	0.987	0.17
(**1**)	C-4	0.94 ± 0.05	−0.58 ± 0.44	10	0.988	0.17
(**1**)	C-5	0.95 ± 0.02	0.06 ± 0.64	10	0.997	0.08
(**2**)	C-2	1.01 ± 0.04	−0.92 ± 0.26	9	0.995	0.11
(**2**)	C-4	0.97 ± 0.03	−0.19 ± 0.18	9	0.998	0.08
(**2**)	C-5	0.97 ± 0.02	−0.20 ± 0.42	9	0.999	0.05
(**3**)	C-3	1.10 ± 0.05	−1.21 ± 0.25	8	0.993	0.13
(**3**)	C-4	0.96 ± 0.01	−0.43 ± 0.30	8	0.999	0.04
(**3**)	C-5	0.93 ± 0.03	−1.12 ± 0.44	8	0.996	0.10
(**4**)	C-3	1.09 ± 0.06	−0.98 ± 0.27	8	0.992	0.15
(**4**)	C-4	0.97 ± 0.01	−0.53 ± 0.24	8	0.999	0.03
(**4**)	C-5	0.96 ± 0.03	−0.50 ± 0.40	8	0.997	0.09

[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, see S. Ehrenson, *J. Org. Chem.*, 1979, **44**, 1793.

Indeed, in each series the total range in SCS values is <4 p.p.m., but the variations of the observed chemical shifts are systematic and clearly electronic in origin. In fact, it can be observed that electron-withdrawing substituents cause upfield shifts of the carboxy resonance, whereas both methyl and methoxy in the '*para*' series and alkyl groups in the '*meta*' series induce downfield shifts. Similar reverse SCS effects have also been noticed on the α-carbon chemical shifts in styrenes,[13] benzonitriles,[14] carbonyl benzene derivatives,[15] and *N*-benzylideneanilines.[16]

To ascertain the nature of the influence on ^{13}C chemical shifts of the interactions between the substituents and the carboxylic group we have attempted some l.f.e. correlations. We observed for the '*para*' series that the correlation of induced SCSs on carboxylic carbon atoms of acids (**1**) and of the corresponding anions (**2**), with the pK_a values of acids (**1**), were unsatisfactory (Table 6, lines 1 and 2); similar results were obtained with Hammett's σ values[17] (Table 6, lines 3 and 4). This is consistent with the fact that ^{13}C chemical shifts and pK_a values are related to different electronic densities, depending on the π-electron density on the carboxy carbon atom and on the total electron density of the carboxy group, respectively. It is obvious that the substituents could affect in some different way the two electronic densities, especially when conjugative interactions are possible (in fact in the '*meta*' isomers the situation is different, see below). For example an electron-withdrawing substituent reduces both π and total electron densities of the carboxy group but increases the electron density on the carboxylic carbon atom.

Better results ($r > 0.95$) were obtained in the cross-correlation of SCS values in acid and anionic '*para*' series and in the correlation between SCS values differences of both series [SCS(**1**) − SCS(**2**)] and pK_a values (Table 6, lines 5 and 6, respectively).

With the same treatments '*meta*' compounds furnished good linear correlations (Table 6, lines 7—12). This different behaviour is consistent with the different role played by the conjugative effects in each series. The goodness of the cross-correlations in both '*meta*' and '*para*' series (Table 6, lines 5 and 11) points out that the substituents in acid and anionic series exert effects of the same kind in determining the π-electron density and the total electron density.†

Moreover, the slope values greater than unity observed in the cross-correlations (1.46 ± 0.15 and 1.46 ± 0.03, respectively)

* A Yukawa–Tsuno treatment of pK_a values for 5-substituted thiophene-2-carboxylic acids showed the occurrence of a small extra-conjugative contribution (r^+ +0.12).[10]

† This viewpoint is confirmed by the observation that in DSP analysis (see below) the acids and the anions require the same kind of substituent constants.

Table 6. Relationships[a] of induced SCSs of carboxylic carbon atoms of acids (**1**) and (**3**) or anions (**2**) and (**4**)

Series	$s + s_s$	$i + s_i$	n	r	f
SCS(**1**)	$(-1.69 \pm 0.46)(-\Delta pK_a)$	$-(0.43 \pm 0.18)$	11	0.772	0.50
SCS(**2**)	$(-3.15 \pm 0.43)(-\Delta pK_a)$	$-(0.61 \pm 0.17)$	10	0.932	0.28
SCS(**1**)	$(-1.72 \pm 0.45)\sigma_p$	$-(0.40 \pm 0.18)$	11	0.786	0.49
SCS(**2**)	$(-3.16 \pm 0.40)\sigma_p$	$-(0.55 \pm 0.16)$	10	0.939	0.26
SCS(**2**)	(1.46 ± 0.15)SCS(**1**)	$-(0.02 \pm 0.17)$	10	0.961	0.31
SCS(**1**) − SCS(**2**)	$(1.32 \pm 0.15)(-\Delta pK_a)$	(0.14 ± 0.06)	10	0.951	0.27
SCS(**3**)	$(-2.77 \pm 0.13)(-\Delta pK_a)$	$-(0.04 \pm 0.05)$	10	0.991	0.14
SCS(**4**)	$(-4.03 \pm 0.23)(-\Delta pK_a)$	$-(0.11 \pm 0.08)$	10	0.988	0.18
SCS(**3**)	$(-2.81 \pm 0.15)\sigma_m$	$-(0.03 \pm 0.05)$	10	0.989	0.17
SCS(**4**)	$(-4.10 \pm 0.22)\sigma_m$	$-(0.09 \pm 0.08)$	10	0.989	0.16
SCS(**4**)	(1.46 ± 0.03)SCS(**3**)	$-(0.05 \pm 0.03)$	10	0.999	0.06
SCS(**3**) − SCS(**4**)	$(1.26 \pm 0.11)(-\Delta pK_a)$	$-(0.07 \pm 0.04)$	10	0.970	0.27
SCS(**pB**)[b]	$(-1.08 \pm 0.17)\sigma_p$	$-(0.54 \pm 0.04)$	12	0.895	0.35
SCS(**mB**)[b]	$(-2.86 \pm 0.23)\sigma_m$	$-(0.04 \pm 0.08)$	12	0.969	0.22

[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; σ values from ref. 17. [b] Values relative to *para*- (**pB**) or *meta*-substituted (**mB**) benzoic acids from ref. 15.

Table 7. DSP analysis[a] of SCS data for carboxylic carbon atoms according to equation (2)

Series	$\rho_I \pm s_\rho$	$\rho_R \pm s_\rho$	Scale[b]	n	r	f	$i \pm s_i$
(**1**)	-2.86 ± 0.31	0.42 ± 0.40	(BA)	10[c]	0.961	0.19	0.02 ± 0.13
(**2**)	-4.23 ± 0.24	-1.16 ± 0.33	(BA)	9[c]	0.992	0.09	-0.10 ± 0.10
(**3**)	-2.81 ± 0.15	-0.74 ± 0.13	(BA)	10	0.994	0.08	-0.03 ± 0.05
(**4**)	-4.11 ± 0.24	-1.10 ± 0.21	(BA)	10	0.993	0.10	-0.09 ± 0.08
p-Benzoic acid[d]	−2.3	−0.5	(BA)				
m-Benzoic acid[d]	−2.8	−0.5	+				

[a] ρ, susceptibility constant; s_ρ and s_i, standard deviations; n, number of points; r, correlation coefficient; f, goodness of the fit; i, intercept. [b] The values of σ are shown in Table B of SUP 56669. [c] Data relative to (**1o**) and (**2o**) have been excluded from the calculations. [d] Ref. 15.

indicate that the carboxylate group is more sensitive to the substituent effects than the carboxylic group in both '*para*' and '*meta*' series.

para- and *meta*-substituted benzoic acids showed (Table 6, lines 13 and 14) a behaviour analogous to that observed with '*para*' and '*meta*' substituted thiophene-2-carboxylic acids when the SCSs of carboxy carbon atoms were correlated with Hammett's σ values.[17]

In order to calculate separately the transmission coefficients for resonance and polar effects we have analysed our data by the DSP equation (1), selecting $\sigma_{(BA)}$ and σ_R^+ which gave the best fit * for the analysis of SCS data of carboxylic (Table 7) and endocyclic carbon atoms, respectively, for the four series of compounds. This agrees with the previously observed occurrence of cross-correlations (Table 6, lines 5 and 11).

Now if we examine the substituent effects on the carboxy and on the endocyclic carbon atom which carries the carboxy group we observe an inversion in the sign of ρ_I on going from C-2 to C-α, in accord with the hypothesis that the substituents affect the π-electron densities of both the aromatic ring and the carboxylic group separately. An analogous inversion has been observed in the case of ρ_R values.

Similar inversions can be observed if the SCS data of Brownlee and his co-workers[14,15] on benzonitriles and some series of ArCOX compounds are analysed by the DSP treatment.

On the transmission of the substituent effects on C-α the values of the susceptibility constants point out that the polar component predominates ($\rho_I > \rho_R$). The ρ_I values calculated in each series (acids and anions, respectively; see Table 7) are constant; their negative sign indicates the occurrence of a reverse SCS effect and agrees with the hypothesis that the inductive component of the carboxy carbon chemical shift is almost exclusively controlled by the π-polarization[19] of the CO π-electrons induced by the dipole of the substituent (**7**).

Moreover ρ_I values of anions [(**2**) and (**4**) series: ρ_I −(4.1—4.2)] are higher than those of acids [(**1**) and (**3**): ρ_I −(2.8—2.9)]: the greater polarizability of carboxylate carbon atom compared with carbon atom of the undissociated carboxy group well accounts for this behaviour. In addition, ρ_I values of carboxylic acids [(**1**) and (**3**) series] and of various carbonyl benzene derivatives [ρ_I −(2.3—3.0)][14] are similar. If the value of '*para*' substituted thiophene-2-carboxylic acids (ρ_I −2.9) can be definitively considered higher than that of *para*-substituted benzoic acids (ρ_I −2.3) this fact can be considered consistent with a better transmission of the substituent effects in the heterocyclic ring.[20] This fact can be related to a geometric factor (the shorter distance between the two substituents in thiophene with respect to benzene derivative) which favours the dipole gradient.

The transmission of resonance effects seems to be more efficient in the thiophene than in the benzene ring and in the anionic rather than in the acid series (see also above for inductive effects). The negative sign of the ρ_R values of either '*meta*' substituted acids (**3**) and both series of '*meta*' and '*para*' substituted anions [(**2**) and (**4**)] can be associated with a major contribution of canonical structures where conjugative interactions between the substituent and the carboxy group through the π-aromatic system are not relevant.

* We have also carried out a DSP analysis of ^{13}C chemical shifts by using the 'universal' inductive and resonance constants according to Afanas'ev,[18] but the statistical results of correlation analysis are worse than those obtained by the selected σ values.[7] Moreover the different kinds of electronic interactions are no longer evident (*e.g.*, see comparison between analysis of SCS data of carboxy and endocyclic carbon atoms).

In contrast, in the '*para*' substituted acids (**1**) is rather difficult to rationalize the ρ_R value.* It is very low and affected by an uncertainty equal to its positive value ($\rho_R \pm s_\rho$ 0.4 ± 0.4).

Perhaps in the anionic species [(**2**) and (**4**)] high internal conjugation $\left(-C\lessdot^{O}_{O^-} \longleftrightarrow C\lessdot^{O^-}_{O}\right)$ is able to interrupt conjugation with the substituted ring; on the other hand in the free acids [(**1**) and (**3**)], where lower internal conjugation $\left(-C\lessdot^{O}_{OH} \longleftrightarrow -C\lessdot^{O^-}_{OH^+}\right)$ occurs, the situation must be different if the substituent is '*meta*' or '*para*', as the calculated susceptibility constants show.

The previous interpretation of the observed values of the susceptibility constants calculated for SCSs of C-α is strengthened by the results of DSP analysis on SCS data (SUP 56669) of C-2 for (**1**)—(**4**) and of C-5 for (**5**) and (**6**). As expected for both (**1**) and (**2**) large and positive susceptibility constants (ρ_I 6.8 and 8.0, ρ_R 16.8 and 17.5, respectively) have been calculated at C-2 (a site conjugated with the substituents);† for both (**3**) and (**4**) also positive susceptibility constants (ρ_I 2.3 and 3.0, ρ_R 3.2 and 3.3, respectively) have been calculated at C-2 but here the absolute values are lower because the site is not conjugated with the substituent. DSP analysis furnishes a similar trend of susceptibility constants for both (**5**) and (**6**).‡

It must be remarked that in the DSP analysis of SCS data of endocyclic carbon atoms for (**1**)—(**6**) the resonance substituent constants are σ_R^+ accordingly with the high conjugative substituent–ring interactions, whereas $\sigma_{(BA)}$ values are conveniently used in the case of carboxy carbon atoms (see above).

Conclusions.—For the examined thiophene series (**1**)—(**4**) the SCS data fitted satisfactorily the DSP equation, indicating that the ^{13}C n.m.r. chemical shifts of both C-α and C-2 are electronic in origin. In determining the SCSs of C-α the inductive effects of the substituent are predominant and the reverse inductive contribution is largely determined by localized π-polarization of the CO π-electrons. The through-resonance interactions play the same feeble role observed in substituted benzoic acids. Nevertheless, in the '*para*' series (**1**) and (**2**) the conjugative effects seem responsible of the unsatisfactory correlations between spectroscopic and equilibrium (pK_a) data; in fact the '*meta*' compounds (**3**) and (**4**) give good correlations.

Resonance effects are predominant in determining the SCSs of endocyclic carbon '*para*' to the present substituent [C-2 in (**1**) and (**2**), C-5 in (**5**)], whereas both resonance and inductive effects operate at an endocyclic carbon '*meta*' to the substituent [C-2 in (**3**) and (**4**); C-5 in (**6**)] even if to a minor extent only.

Experimental

Spectroscopic Measurements.—^{13}C N.m.r. spectra were run at 20 MHz on a Varian FT-80A pulsed Fourier transform spectrometer in CD_3OD solutions with Me_4Si as internal standard. The smallest convenient spectral width and a sufficient number of data points were used to acquire the spectra so that maximum digital resolution was obtained (generally 5 kHz and 16 K, respectively). Pulse width of 12 μs and pulse delay variable from 3 to 10 s were selected, the transients number depending on the concentration. The chemical shift values were measured from fully decoupled spectra. Peaks assignment was performed by examination of substituent shifts and occasionally off-resonance decoupled or proton coupled spectra. Concentrations of 0.1—0.2M were used for the sample solutions. The effect of the dilution was checked, for compounds (**1b**, **d**, **i**, and **m**) and (**3b**), by examination of spectra performed at decreasing concentrations to 0.01M and no sizeable variations occurred in the ^{13}C chemical shifts. We prepared anionic solutions by addition of amounts of sodium methoxide (*ca.* 3M) to acid solutions and we recorded the spectra until the shifts became constant. This was achieved when an excess (*ca.* 10%) of methoxide was added. For compounds (**2b** and **d**) and (**4b**) it was necessary to employ considerably more dilute (0.01M) solutions, owing to the precipitation of salt when sodium methoxide was added. The spectrum of (**2c**) could not be recorded because of the poor solubility of the compound. 4-Acetylthiophene-2-carboxylic acid (**3d**) was in equilibrium with the hemiacetal form. In compounds (**4a** and **b**) exchange of the proton at C-5 with deuterium occurred.

Synthesis and Purification of Compounds.—5-Nitro-,[21] 5-methylsulphonyl-,[22] 5-carboxy-,[23] 5-acetyl-,[24] 5-bromo-,[25] 5-chloro-,[26] 5-iodo-,[27] 5-methylthio-,[22] 5-methyl-,[28] 5-methoxy-,[29] 4-nitro-,[30] 4-bromo-,[31] 4-fluoro-,[32] 4-methyl-,[33] 4-isopropylthiophene-2-carboxylic acid,[34] and thiophene-2-carboxylic acid[35] were prepared as reported. The other compounds were prepared as below and gave correct elemental analyses.

4-*Methylsulphonylthiophene-2-carboxylic acid* (**3b**). A solution of (**3l**) (0.8 g) in acetic acid (3.8 ml) was refluxed (3 h) with hydrogen peroxide (1.9 ml, 36%). The solution was concentrated at reduced pressure and then poured into cooled water. The precipitate obtained was crystallized from water, m.p. 196—197 °C.

4-*Methylthiothiophene-2-carboxylic acid* (**3l**). Crude 4-methylthiothiophene-2-carbaldehyde (2.6 g) was slowly added at 0—5 °C to a suspension of silver oxide obtained from a solution of silver nitrate (5.7 g) in water (12 ml) by addition of sodium hydroxide (2.7 g in 12 ml of water). Silver was filtered off and the solution acidified with concentrated hydrochloric acid and kept in a refrigerator overnight: the precipitate obtained was filtered off and crystallized from light petroleum–benzene, m.p. 123—124 °C. Acid (**3l**) has been previously synthesized by another route, m.p. 115 °C.[36]

4-*Methylthiothiophene-2-carbaldehyde.* A suspension of crude 2-(4-methylthio-2-thienyl)-1,3-dioxolane (2.9 g) in 5% hydrochloric acid (38 ml) was heated at 80 °C under stirring for 5 h. The cooled suspension was extracted with diethyl ether. The ethereal extracts were washed with water and dried (Na_2SO_4). After evaporation of ether, the residue was chromatographed on silica gel using light petroleum–benzene (1:1) as eluant.

2-(4-*Methylthio-2-thienyl*)-1,3-*dioxolane.* A solution of 2-(4-lithio-2-thienyl)-1,3-dioxolane [obtained from 2-(4-bromo-2-thienyl)-1,3-dioxolane[23] (32.2 g) in anhydrous diethyl ether (140 ml) by action of n-butyl-lithium (108 ml, 1.3N) at −70 °C] was added with stirring to a solution of dimethyl disulphide (13.2 g) in anhydrous ethyl ether (66 ml). After stirring (3 h) the solution was poured into cold water. The ethereal phase was washed with dilute sodium hydroxide solution and with water, and dried ($CaCl_2$). The residue oil was distilled at reduced pressure and immediately hydrolysed.

4-*Acetylthiophene-2-carboxylic acid* (**3d**). A solution of 2-(2-

* It should be noted that it has been necessary to exclude the data for the 5-methoxy-substituted derivatives (**1o**) and (**2o**) from the correlation (Table 7, lines 1 and 2). We believe that this substituent deviates because of its strong conjugative effect which increases, relative to other substituents, the contribution of canonical structures involving conjugative transfer of π-electron density between the substituent and the heteroaromatic ring.

† As suggested by a referee, our interpretation would have been supported by the DSP analysis of SCS data for C-α and C-1 of benzoic acids. Since these data are lacking, we have applied the DSP analysis to the data for the corresponding methyl esters and observed, accordingly, for C-α, ρ_I 2.6 and ρ_R −1.1 and for C-1, ρ_I 4.0 and ρ_R 8.0, respectively.

‡ For the correlations involving compounds (**5**) and (**6**) the following substituents were used: OMe, Me, H, F, Cl, Br, Ac, CO_2H, CO_2Me, CN, and NO_2.

bromo-4-thienyl)-2-methyl-1,3-dioxolane (18.6 g) in anhydrous diethyl ether (124 ml) was added rapidly with stirring to a solution of n-butyl-lithium (58.6 ml, 1.6M) in anhydrous ethyl ether (15 ml) at −70 °C. After a few minutes the mixture was poured into a suspension of solid carbon dioxide in anhydrous diethyl ether. When the temperature reached −15 °C, the mixture was poured into water (100 ml), and the ethereal phase was extracted with an aqueous solution of sodium hydroxide. The combined aqueous phases were acidified with concentrated hydrochloric acid and left overnight under stirring. The solid formed was filtered off and crystallized from methanol, m.p. 164 °C. Acid (**3d**) has been previously synthesized by another route, m.p. 165 °C.[37]

2-(2-*Bromo*-4-*thienyl*)-2-*methyl*-1,3-*dioxolane*. A solution of 2-bromo-4-acetylthiophene (19.6 g), ethylene glycol (7.5 g), and some crystals of toluene-*p*-sulphonic acid in benzene (25.4 ml) was refluxed with a water separator until no water separated (*ca.* 20 h). The benzene layer was washed with aqueous sodium hydrogencarbonate and with water, and then dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue oil was distilled *in vacuo*.

4-*Methoxythiophene*-2-*carboxylic acid* (**3o**). A solution of methyl ester[38] (1 g) of acid (**3o**) in methanol (80 ml) and sodium hydroxide (20 ml, 1N) was kept at 40 °C for 170 h. The solvent was removed at reduced pressure and the residue diluted with water and extracted with ethyl ether. The ethereal extracts were dried (Na_2SO_4) and, after evaporation of the solvent, the crude acid was crystallized from benzene, m.p. 164 °C.

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