MAGNETIC RESONANCE IN CHEMISTRY, VOL. 33, 883–888 (1995)

Analysis of ^{13}C NMR Substituent Chemical Shifts in Some (Aryl)(2-nitrobenzo[*b*]thiophen-3-yl)amines: a New Class of Compounds with Analgesic, Anti-Exudative and Anti-Inflammatory Activities Showing Low Mutagenicity

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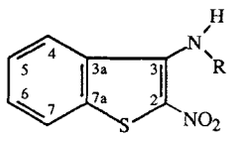
The ^{13}C NMR chemical shift values of (aryl)(2-nitrobenzo[*b*]thiophen-3-yl)amines were measured in DMSO-d_6 solutions, suggesting the occurrence of an alternate charge polarization at C-3, C-2, C-3a, C-7a, C-4 and C-5. A dual substituent parameter analysis of the experimental data indicates a large or a low resonance contribution for aryl *para* or *meta* substituents, respectively, while the inductive component remains constant throughout.

KEY WORDS ^{13}C NMR; substituent chemical shifts; anilines; (aryl)(2-nitrobenzo[*b*]thiopen-3-yl)amines; alternate charge polarization

INTRODUCTION

The gastrointestinal tolerance of anti-inflammatory agents represents a real pharmacological problem. In view of this fact, non-acid and non-steroidal drugs[1] are gaining increasing interest. Recently, we reported on the analgesic, anti-exudative and/or anti-inflammatory activities of several *N*-substituted 3-amino-2-nitrobenzo[*b*]thiophenes[2] (**1**, R = alkyl or aryl); some of these show promising pharmacological activity and, at the same time, a low mutagenic activity, as measured by the Ames test.[3] Interestingly, compounds **1*p*-e** and **-f**, i.e., those which showed the largest activities in the series studied,[2b] were non-mutagenic.[3]



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1*p*: R = *p*-XC_6H_4
1*m*: R = *m*-XC_6H_4

a; X = H	**e**; X = Cl	**i**; X = OH
b; X = NO_2	**f**; X = Br	**j**; X = OMe
c; X = CN	**g**; X = F	**k**; X = NMe_2
d; X = CF_3	**h**; X = Me	**l**; X = NEt_2

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Many factors could affect either mutagenic or pharmacological activities and both polarographic and biological (nitro)reductions depended on the structure of the organic skeleton to which the nitro group was linked. Thus, in the framework of our previous studies on the use of ^{13}C NMR spectroscopy to collect information on the transmission of substituent effects in aromatic[4] and heteroaromatic[5] compounds, we carried out a ^1H and ^{13}C NMR study of compounds **1*p*** and **1*m*** to acquire information on their electronic density distribution.

EXPERIMENTAL

NMR measurements

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer operating in the Fourier transform (FT) mode at 250.13 and 62.90 MHz, respectively, in DMSO-d_6 solutions at concentrations of 0.02 and 0.1 M, respectively. ^1H and ^{13}C chemical shift values were measured relative to TMS (as internal standard) and DMSO-d_6 (chemical shift of the central peak at 39.50 ppm downfield from TMS), respectively. ^{13}C NMR chemical shift values were measured from proton fully decoupled spectra. Signal assignments were made on the grounds of both known substituent effects and multiplicities determined by either DEPT-135 or 'proton gated' decoupled experiments and confirmed by

CCC 0749–1581/95/110883–06
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Received 3 March 1995
Accepted 16 June 1995

either homonuclear and heteronuclear selective experiments or 2D C,H correlation experiments. Typical conditions for ^{1}H NMR spectra were as follows: spectral width, 3250 Hz; number of data points, 16K, giving a digital resolution of 0.4 Hz per point; pulse width, 6.5 μs (flip angle 90°); and acquisition time, 2.5 s. No exponential line broadening function was used. Typical conditions for ^{13}C NMR spectra were as follows: spectral width, 12 600 Hz; number of data points, 32K (zero-filled to 64K), giving a digital resolution of 0.4 Hz per point; pulse width 3 μs (flip angle of 90° was 6.3 μs); acquisition time 1.3 s; relaxation delay, varied from 2.6 to 6 s; and number of scans, 1K. Exponential multiplication equivalent to a line broadening of 1.0 Hz was applied to the FIDs before Fourier transformation. Two-dimensional NMR experiments were performed using the standard Bruker pulse sequences XHDEPT.AUR and COLOC.AUR, for one-bond (160 Hz) and long-range (7.5 Hz) C,H interactions, respectively.

Synthesis and purification of compounds

Amines **1*p*-a**, **-d**, **-e**, **-g**, **-i**,[2b] **-k** and **-l**,[2a] and **1*m*-d** and **-e**[2b] were prepared and purified according to literature methods: **1*p*-c**,**-f**,**-h** and **-j** and **1*m*-b**,**-f**,**-g**,**-h**,**-i**,**-j** and **-k** were synthesized from 3-bromo-2-nitrobenzo[*b*]thiopene (2.58 g, 10 mmol) and the appropriate amine (30 mmol) by refluxing for 5–20 min in *N*,*N*-dimethylformamide (30 cm^3) in the presence of triethylamine (2.51 cm^3, 18 mmol). The reaction mixtures were worked up as reported previously.[6] Melting points and crystallization solvents for the new compounds [for which satisfactory analyses (C, H, N and S) were obtained] are reported in the footnotes of Tables 1 and 2.

RESULTS AND DISCUSSION

Craik and Brownlee,[7] Exner and Buděšínský,[8] Dell'Erba *et al.*[9] and Spinelli *et al.*,[5] measured the ^{13}C NMR substituent chemical shift (SCS) values of several series of mono- and polysubstituted benzenes and thiophenes to gain information on the additivity of the substituent effects and on the use of linear free energy (l.f.e.) treatments of data to study the relationships between ^{13}C SCS values and the electronic effects of substituents. Because of the superimposition of anisotropy, resonance and inductive effects,[10] the SCS values relevant to the carbon atoms of the aromatic ring usually do not furnish mono- (Hammett) or biparametric [dual substituent parameter (DSP)][11] l.f.e. relationships.

Further, we have determined the ^{13}C SCS values of several 5-nitrothiopene-3-carboxanilides (a novel group of direct-acting mutagens)[12] to gain information on the kind of substituent effect transmission via the amide bond (—CO—NH—Ar), i.e., a system of great biological interest. In order to extend this analysis to other compounds showing biological activity, we have now studied the behaviour of several (aryl)(2-nitrobenzo[*b*]thiophen-3-yl)amines (**1*p*-a** and **-c**–**l** and **1*m*-a**, **-b** and **-d**–**k**).

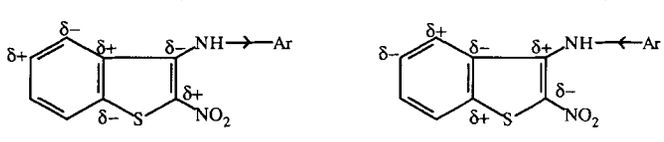
In the **1*p*** series, the ^{13}C NMR chemical shift values (Table 1) of C-3 were significantly (SCS range 8.74 ppm) shielded and deshielded by electron-withdrawing and -donating substituents, respectively. An opposite effect was observed on C-2 and C-3a, with a high (SCS range 10.11 ppm) and a low (SCS range 2.64 ppm) susceptibility to the substituent effect, in agreement with the hyper-[13] and hypo-*ortho*[13a,b,h,14] character of the C-3—C-2 and C-3–C-3a bonds, respectively. Lower SCS variations were observed for more distant carbon atoms (SCS range 1.64 ppm for C-7a, 1.26 for C-4 and 0.96 for C-5), all reflecting an alternate charge polarization.[12,15] Thus, the effect exerted by an electron-withdrawing or -donating substituent on the electron distribution, as judged by the chemical shift values, could be depicted as in Scheme 1. The very small variations on both C-6 and C-7 (SCS ranges 0.46 and 0.29 ppm, respectively) appeared random.

A similar trend of the substituent-induced chemical shift variations was observed in **1*m*** (Table 2) but with a smaller susceptibility than for **1*p***, as expected for electronic effects from a *meta*-position compared with effects from a *para*-position. Moreover, the occurrence of the alternate charge polarization was confirmed. Again, the variations on C-6 and C-7 were very small (SCS ranges 0.18 and 0.27 ppm, respectively) and random.

A representative picture of the alternate charge polarization showing the different susceptibilities of the various carbon atoms to the substituent effect could be obtained by means of cross-correlations, e.g., by plotting SCS values concerning C-2, C-3a, C-7a, C-4 and C-5 versus those of C-3, i.e., of the carbon atom on which the variable arylamino group directly exerted its electronic effects. The alternating negative and positive slopes of such correlations (expected on the basis of Scheme 1) are summarized in Scheme 2 for **1*p*** ($r = 0.945$–0.996) and **1*m*** ($r = 0.953$–0.9994) and furnished a clear picture of the progressive attenuation of the electronic effects of X, which appeared similar for the two series of compounds.

The sizeable effect of the X groups on the chemical shifts of the carbon atoms of the benzo[*b*]thiophene skeleton confirmed the ability of the nitrogen atom of anilines (or of their derivatives)[12,16,17] as a good bridge for the transmission of such effects.

As far as the anilino group itself was concerned, in both **1*p*** and **1*m*** the SCS values of carbon atoms *ipso*, *ortho* and *para* to X were large, whereas those for the *meta* carbon atoms were low, in good agreement with previous observations relevant to *para*- and *meta*-substituted anilines.[17] Accordingly, cross-correlations with the SCS of the corresponding *para*- and *meta*-



Scheme 1. Representation of the alternate charge polarization on carbon atoms of the benzo[*b*]thiophene skeleton in **1** as determined by electron-withdrawing and -donating substituents.

Table 1. ^{13}C NMR SCS values [in ppm with respect to the unsubstituted compound (X = H) for which chemical shifts in ppm are relative to DMSO-d_6 centred at 39.50 ppm (with respect to Me_4Si)] and ^{1}H NMR chemical shifts (figures in parentheses, in ppm with respect to internal Me_4Si) of **1***p*

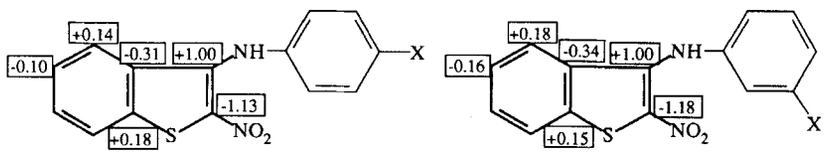
Derivative	X, ΔSCS[a]	C-2 10.11	C-3 8.74	C-3a 2.64	C-4 1.26	C-5 0.96	C-6 0.46	C-7 0.29	C-7a 1.64	C-1′ 19.33	C-2′,6′ 7.87	C-3′,5′ 21.35	C-4′ 55.94	NH
a	H	124.42	142.71	129.35	126.19	124.59	130.72	123.78	137.49	139.26	124.19	129.18	126.21	
					(7.11)	(7.21)	(7.59)	(7.95)			(7.34)	(7.44)	(7.33)	(10.45)
c	CN[b,c]	7.08	−5.75	1.98	−0.69	0.74	−0.06	−0.08	−1.03	5.99	−4.77	3.86	−21.94	
					(7.81)	(7.47)	(7.69)	(8.06)			(7.21)	(7.76)		(10.38)
d	CF_3[d,e]	5.34	−4.40	1.48	−0.64	0.50	−0.15	−0.13	−0.88	4.95	−3.90	−3.26	−2.73	
					(7.70)	(7.41)	(7.66)	(8.03)			(7.29)	(7.67)		(10.32)
e	Cl	−0.17	−1.35	0.51	−0.12	0.38	0.10	0.14	−0.19	−0.45	0.67	−0.16	3.21	
					(7.33)	(7.32)	(7.62)	(7.98)			(7.30)	(7.46)		(10.34)
f	Br[f]	1.94	−1.65	0.56	−0.18	0.35	0.06	0.09	−0.25	0.02	0.75	2.70	−8.78	
					(7.39)	(7.32)	(7.62)	(7.98)			(7.24)	(7.58)		(10.32)
g	F	−0.39	0.30	−0.18	−0.06	0.06	−0.04	−0.02	0.03	−3.65	2.40	−13.27	34.00	
					(7.06)	(7.23)	(7.58)	(7.95)			(7.41)	(7.29)		(10.43)
h	Me[g,h]	−0.94	0.73	−0.32	0.07	−0.13	−0.03	−0.09	0.13	−2.90	0.40	0.49	9.80	
					(7.07)	(7.19)	(7.57)	(7.93)			(7.26)	(7.26)		(10.45)
i	OH	−2.46	2.45	−0.66	0.35	−0.17	0.07	−0.08	0.42	−9.56	3.10	−13.30	30.53	
					(6.89)	(7.15)	(7.54)	(7.89)			(7.22)	(6.86)		(10.49)
j	OMe[i,j]	−1.83	1.80	−0.53	0.19	−0.10	0.03	−0.04	0.31	−7.82	2.71	−14.69	31.97	
					(6.93)	(7.17)	(7.56)	(7.92)			(7.34)	(7.03)		(10.50)
k	NMe_2[k]	−2.79	2.61	−0.63	0.57	−0.22	0.04	−0.15	0.41	−12.79	2.33	−16.94	23.28	
					(6.98)	(7.16)	(7.55)	(7.90)			(7.23)	(6.79)		(10.53)
l	NEt_2[l]	−3.03	2.99	−0.47	0.53	−0.01	0.31	0.61	0.61	−13.34	2.89	−17.49	20.63	
					(7.02)	(7.18)	(7.56)	(7.91)				(7.20)	(6.74)	(10.53)

[a] SCS range in ppm.
[b] *C*N 119.09 ppm.
[c] M.p. 219–220°C, from ethyl acetate.
[d] *C*F_3 124.27 ppm.
[e] Data from Ref. 6.
[f] M.p. 201–202°C, from ethanol.
[g] *C*H_3 20.47 ppm; *CH*$_3$ 2.37 ppm.
[h] M.p. 154–155°C, from cyclohexane.
[i] O*C*H_3 55.30 ppm; O*CH*$_3$ 3.82 ppm.
[j] M.p. 193–194°C, from ethanol.
[k] N(*C*H_3)$_2$ 39.74 ppm; N(*CH*$_3$)$_2$ 2.97 ppm.
[l] N(*C*H_2CH$_3$)$_2$ 43.76 ppm; N(CH$_2$*C*H_3)$_2$ 12.31 ppm; N(*CH*$_2$CH$_3$)$_2$ 3.38 ppm; N(CH$_2$*CH*$_3$)$_2$ 2.12 ppm.

Table 2. ^{13}C NMR SCS values [in ppm with respect to the unsubstituted compound (X = H) for which chemical shifts in ppm are relative to DMSO-d_6 centred at 39.50 ppm (with respect to Me_4Si)] and ^1H NMR chemical shifts (figures in parentheses, in ppm with respect to internal Me_4Si) of 1*m*

Derivative	X. ΔSCS[a]	C-2 5.77	C-3 4.93	C-3a 1.77	C-4 0.95	C-5 0.90	C-6 0.18	C-7 0.27	C-7a 0.74	C-1′ 2.78	C-2′ 16.81	C-3′ 40.64	C-4′ 17.07	C-5′ 1.85	C-6′ 14.86	NH
a	H	124.42	142.71	129.35	126.19	124.59	130.72	123.78	137.49	139.26	124.19	129.18	126.21	129.18	124.19	
					(7.11)	(7.21)	(7.59)	(7.95)			(7.34)	(7.44)	(7.33)	(7.44)	(7.34)	(10.45)
b	NO_2[b]	4.78	−3.99	1.39	−0.52	0.66	0.06	0.06	−0.66	2.59	−9.08	18.88	−7.94	0.88	2.69	
					(7.67)	(7.40)	(7.67)	(8.05)			(8.03)		(7.99)	(7.62)	(7.56)	(10.44)
d	CF_3[c,d]	3.46	−2.90	0.89	−0.54	0.32	−0.07	0.01	−0.47	1.74	−5.83	0.52	−5.43	0.78	1.28	
					(7.46)	(7.34)	(7.63)	(8.01)			(7.60)		(7.53)	(7.59)	(7.46)	(10.38)
e	Cl	2.70	−2.29	0.62	−0.41	0.24	−0.12	−0.05	−0.45	2.21	−2.00	4.07	−1.53	1.21	−3.28	
					(7.41)	(7.33)	(7.63)	(7.99)			(7.36)		(7.29)	(7.37)	(7.19)	(10.31)
f	Br[e]	2.68	−2.18	0.70	−0.29	0.34	0.01	0.07	−0.32	2.40	0.96	−7.51	1.47	1.59	−2.70	
					(7.41)	(7.33)	(7.63)	(7.99)			(7.51)		(7.41)	(7.34)	(7.24)	(10.32)
g	F[f]	2.55	−1.98	0.71	−0.23	0.35	0.03	0.08	−0.34	2.58	−14.45	33.13	−14.46	1.38	−5.48	
					(7.42)	(7.33)	(7.63)	(8.00)			(7.15)		(7.08)	(7.42)	(7.10)	(10.33)
h	Me[g,h]	−0.10	0.14	−0.08	0.01	0.07	−0.05	−0.08	−0.01	−0.19	0.31	9.54	0.71	−0.26	−2.90	
					(7.13)	(7.22)	(7.59)	(7.96)			(7.19)		(7.13)	(7.33)	(7.17)	(10.41)
i	OH[i]	−0.04	0.13	−0.07	0.19	−0.05	−0.04	−0.13	−0.04	0.87	−13.03	28.89	−12.68	0.70	−9.32	
					(7.23)	(7.24)	(7.59)	(7.94)			(6.76)		(6.77)	(7.24)	(6.77)	(10.32)
j	OMe[j,k]	0.47	−0.29	−0.02	0.02	−0.09	−0.10	−0.16	−0.11	1.09	−14.55	30.71	−14.32	0.63	−8.11	
					(7.23)	(7.24)	(7.60)	(7.95)			(6.97)		(6.90)	(7.34)	(6.90)	(10.38)
k	NMe_2[l,m]	−0.99	0.94	−0.38	0.41	−0.24	0.02	−0.19	0.08	0.10	−15.85	21.95	−15.60	0.28	−12.17	
					(7.19)	(7.20)	(7.58)	(7.93)			(6.76)		(6.72)	(7.24)	(6.62)	(10.44)

[a] SCS range in ppm.
[b] M.p. 191–192°C, from ethanol.
[c] CF_3 123.89 ppm.
[d] Data from Ref. 6.
[e] M.p. 167–168°C, from ethanol.
[f] M.p. 194–195°C, from ethanol.
[g] CH_3 20.70 ppm; CH_3 2.32 ppm.
[h] M.p. 154–155°C, from ethanol.
[i] M.p. > 250°C (decomp.), from ethanol.
[j] OCH_3 55.15 ppm; OCH_3 3.82 ppm.
[k] M.p. 159–160°C, from ethanol.
[l] $N(CH_3)_2$ 39.75 ppm; $N(CH_3)_2$ 2.90 ppm.
[m] M.p. 165–166°C, from cyclohexane.



1*p* **1*m***

Scheme 2. Figures on the carbon atoms represent the relative susceptibilities to the substituent effects taking as reference the effect on C-3.

substituted anilines were usually excellent, with slopes near to unity for the *ipso* and *ortho* carbon atoms ($s = 0.94$–1.00, $r \geq 0.993$), while carbon atoms *para* to the substituent furnished slopes significantly higher or lower than unity [$s = 1.27$ and 0.84_5 ($r = 0.998$ and 0.973) for **1*p*** and **1*m***, respectively].

The chemical shift variations of the carbon atoms of the benzo[*b*]thiophene skeleton were also examined by using the Hammett equation or the DSP analysis [Eqn (1)] in order to separate inductive and mesomeric substituent effects.

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

In Eqn (1) (developed by Ehrenson *et al.*[11]), σ_I and σ_R are, respectively, the inductive and resonance substituent constants, ρ_I and ρ_R are the relevant susceptibility constants and i represents the intercept of the regression plane with the SCS axis ($\sigma_I = \sigma_R = 0$).

Table 3 Statistical data[a] for the Hammett analysis of SCS values of carbon atoms of compounds 1*p* and 1*m*

Line	Probe atom	Series	$\rho \pm s_\rho$	Substituent constant	$i \pm s_i$	n[b]	r
1	C-2	**1*p***	7.86 ± 0.69	σ_p^-	−0.57 ± 0.28	10	0.971
2	C-3		−6.78 ± 0.48	σ_p^-	0.46 ± 0.20	10	0.980
3	C-3a		2.19 ± 0.16	σ_p^-	−0.10 ± 0.07	10	0.978
4	C-7a		−1.21 ± 0.09	σ_p^-	0.07 ± 0.04	10	0.977
5	C-4		−0.93 ± 0.10	σ_p^-	0.08 ± 0.04	10	0.959
6	C-5		0.79 ± 0.07	σ_p^-	0.03 ± 0.03	10	0.970
7	C-2	**1*m***	7.23 ± 0.50	σ_m	−0.13 ± 0.17	10	0.982
8	C-3		−6.14 ± 0.44	σ_m	0.18 ± 0.15	10	0.980
9	C-3a		2.12 ± 0.16	σ_m	−0.12 ± 0.05	10	0.978
10	C-7a		−0.94 ± 0.07	σ_m	−0.01 ± 0.02	10	0.979
11	C-4		−1.08 ± 0.19	σ_m	0.11 ± 0.07	10	0.891
12	C-5		0.96 ± 0.14	σ_m	−0.06 ± 0.05	10	0.927

[a] ρ, Susceptibility constant; i, intercept; s_ρ and s_i, standard deviations; n, number of points; r, correlation coefficient.
[b] The used compilation of substituent constants (see Ref. 18) did not contain the datum for X = *p*-NEt_2, which has been excluded from the calculation.

Table 4. Statistical data[a] for the DSP analysis of SCS values of carbon atoms of compounds 1*p* and 1*m*

Line	Probe atom	Series	$\rho_I \pm s_\rho$	$\rho_R \pm s_\rho$	Substituent constants	$i \pm s_i$	n[b]	
1	C-2	**1*p***	7.87 ± 1.00	9.15 ± 0.72	σ_I, σ_R^-	0.36 ± 0.42	10	0.986
2	C-3		−7.20 ± 0.78	−7.61 ± 0.56	σ_I, σ_R^-	−0.14 ± 0.33	10	0.988
3	C-3a		2.38 ± 0.28	2.43 ± 0.20	σ_I, σ_R^-	0.07 ± 0.12	10	0.985
4	C-7a		−1.26 ± 0.15	−1.38 ± 0.11	σ_I, σ_R^-	−0.05 ± 0.06	10	0.986
5	C-4		−1.00 ± 0.18	−1.04 ± 0.13	σ_I, σ_R^-	0.01 ± 0.08	10	0.965
6	C-5		1.07 ± 0.14	0.73 ± 0.10	σ_I, σ_R^-	−0.01 ± 0.06	10	0.972
7	C-2	**1*m***	6.57 ± 0.33	2.77 ± 0.24	σ_I, $\sigma_{R(BA)}$	0.20 ± 0.15	9	0.995
8	C-3		−5.47 ± 0.29	−2.46 ± 0.21	σ_I, $\sigma_{R(BA)}$	−0.16 ± 0.13	9	0.995
9	C-3a		1.87 ± 0.09	0.89 ± 0.06	σ_I, $\sigma_{R(BA)}$	0.02 ± 0.04	9	0.996
10	C-7a		−0.88 ± 0.08	−0.33 ± 0.06	σ_I, $\sigma_{R(BA)}$	−0.04 ± 0.04	9	0.985
11	C-4		−0.80 ± 0.16	−0.60 ± 0.12	σ_I, $\sigma_{R(BA)}$	−0.05 ± 0.07	9	0.953
12	C-5		0.80 ± 0.12	0.48 ± 0.08	σ_I, $\sigma_{R(BA)}$	0.03 ± 0.05	9	0.970

[a] As in Table 3.
[b] The compilation of substituent constants used (see Refs 11 and 18) did not contain the data for X = *p*-NEt_2 or *m*-OH, which have been excluded from the calculations.

The Hammett equation gave the best results by using σ_p^- and σ_m substituent constants for **1*p*** and **1*m***, respectively (Table 3). Any of the four available sets of σ_R,[11,18] on the other hand, could be used in the DSP analysis: as expected from the results of the single-parameter equation, the best correlations were obtained by using the σ_R^- and $\sigma_{R(BA)}$ scales for **1*p*** and **1*m***, respectively (Table 4). Both treatments gave satisfactory correlations for the chemical shifts of C-3, C-2, C-3a, C-7a, C-4 and C-5. Thus, the occurrence of an alternate charge polarization and the higher effect exerted by *para*- with respect to *meta*-substituents was confirmed.

It is noteworthy that the dissection of inductive and resonance effects, allowed by the DSP analysis, showed the expected large variation of λ (ρ_R/ρ_I) on going from *para*- to *meta*-substituted derivatives, a variation which depended on the decreased resonance contribution in **1*m*** with respect to **1*p***, while the inductive component was much less affected in the two series. Further, the fact that the best results were furnished by different substituent constants in the two series (σ^- and σ_m in the Hammett equation, σ_R^- and $\sigma_{R(BA)}$ in the DSP treatment, for *para*- and *meta*-substituted compounds, respectively) agrees with the different nature of the electronic interactions in the two series.

Acknowledgement

Financial support from MURST and CNR is gratefully acknowledged.

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