JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 6, 307–315 (1993)

SUBSTITUENT EFFECTS IN CARBON-13 NMR SPECTRA OF AMINOPYRIDINES

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^{13}C NMR spectra of 45 vicinally substituted 2-, 3- and 4-aminopyridines were investigated. The substituent effects are evidently sensitive to the position of both the substituent and the fixed amino group. In the *para* position with respect to the substituent, long-range electronic effects are expressed by the dual substituent parameter treatment (DSP), and the resonance contribution is more important than the inductive contribution. Correlation results for the *ipso* and *ortho* carbon atoms using the more sophisticated extended DSP equation suggest non-electronic effects of unknown origin.

INTRODUCTION

A fundamental understanding of linear free energy relationships (LFER) in heteroaromatic compounds is of central importance in chemistry and biochemistry.[1,2] Our recent studies[3] on the protonation reaction of vicinally substituted 2-, 3- and 4-aminopyridines showed that localized (inductive/field) and delocalized (resonance) effects are apparently sensitive to the variation of the substituent position in the ring. Thus, the interaction of the substituent in positions 2 and 3 is mainly of inductive character, whereas the substituent in position 4 influences through its resonance effect.[3]

Multinuclear magnetic resonance spectroscopy has been found to be efficient for the investigation of vicinally substituted pyridines from many different points of view.[4–7] The ^{13}C NMR chemical shifts are more sensitive to substituent effects than are reactivity parameters,[8] and allow the simultaneous study of the substituent effect at more than one site in the molecule. It seemed worthwhile to rationalize the substituent chemical shifts (SCSs) of vicinally substituted 2-, 3- and 4-aminopyridines in terms of single and multiple substituent parameter correlation analysis.

EXPERIMENTAL

^{13}C NMR proton-coupled and -decoupled spectra were recorded on a Varian XL-200 spectrometer for approximately 0·2 M solutions in dimethyl sulphoxide–$CDCl_3$ (1:5) with tetramethylsilane as an internal standard, as described previously.[9] Two-dimensional (2D) C–H correlated spectra were obtained on a Bruker AM-500 spectrometer as before.[7]

The assignments were established as previously.[6a,c,d,7,9] The calculated data were obtained by addition of the pyridine substituent increments to the carbon chemical shifts of pyridine.[6a,7,10]

The 2-, 3- and 4-aminopyridines, 2,3- and 3,4-diaminopyridines and 3-amino-2-chloropyridine were commercial samples and were purified before use. Other compounds were obtained according to literature procedures.[3,11] The purity of all pyridines was checked by thin-layer chromatography.

RESULTS AND DISCUSSION

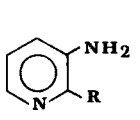
The experimental ^{13}C chemical shifts for carbon atoms of 2-substituted 3-aminopyridines (Series **1**), 4-substituted 3-aminopyridines (Series **2**), 3-substituted 2-aminopyridines (Series **3**) and 3-substituted 4-aminopyridines (Series **4**) are summarized in Tables 1–4.

Deviations from additivity, $\Delta = \delta_{exp} - \delta_{calc.}$, for all ring carbons were calculated and are given in Tables 1–4 in parentheses. The examination of such data is of interest because the possible interactions between the substituent and the fixed amino group and/or ring nitrogen atom can be identified.

Some interesting trends are observed within the Δ values for halogens. Thus, for the *ipso* carbon 3 in Series **4** (Table 4), the Δ values appropriate to R = F, Cl and Br increase in the order F > Cl > Br. This shows that deviations are inductive dependent rather than attributable to the atomic size. In contrast, an

0894–3230/93/050307–09$09.50

Received 17 November 1992
Revised 3 February 1993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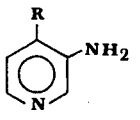
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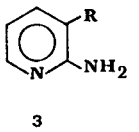
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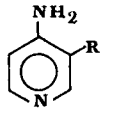
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interesting reversed effect is observed for the *ortho* carbon 3 (Table 1) and for the *ortho* carbon 4 (Table 4) indicative of the anisotropy effect. This may be caused by the proximity of the ring nitrogen atom.

In general, electron-donor and -acceptor groups produce a downfield shift for all *ipso* carbon atoms. Less pronounced upfield shifts are sometimes observed for R = CN, $CONH_2$, CO_2Et, CN, Cl and Br. As seen from Tables 1–4, the ranges of the substituent chemical shifts, ΔSCSs, of *ipso* carbons are the largest. Their narrower range for Series **1** can probably be attributed to the adjacent ring nitrogen atom. Inspection of the SCSs indicates that the substituent exerts an upfield shift on all *ortho* carbon atoms 2, 3 and 4. NMe_2, $CONH_2$ and CO_2Et groups cause an opposite effect in Series **1**, **2** and **4**. The *para* carbon atoms with respect to electron-donor groups absorb at higher field than those in 2-, 3- and 4-aminopyridines. Electron-withdrawing substituents other than halogens produce a downfield shift. The observed irregularity suggests that the SCSs cannot be rationalized on the basis of the electronic properties of the particular group alone.

A reasonably good cross-correlation of the chemical shifts in Series **4** vs those in Series **3** was obtained for the *ipso* carbon 3 [slope $A = 0{\cdot}93$ ($\pm 0{\cdot}07$), correlation coefficient $r = 0{\cdot}982$, standard deviation $s = 1{\cdot}384$] and for *para* carbon 6 [$A = 0{\cdot}58$ ($\pm 0{\cdot}06$), $R = 0{\cdot}964$,

Table 1. ^{13}C NMR chemical shifts (experimental and calculated)[a] (δ, ppm) of 2-substituted 3-aminopyridines

R	C-2	C-3	C-4	C-5	C-6	Others	
	136·77	142·99	121·19	123·52	138·77		
H	(0·84)	(−2·23)	(−0·55)	(−1·10)	(−2·26)		
	143·22	140·43	121·74	120·67	138·47	19·41	
Me[b]	(−3·26)	(−4·28)	(−0·28)	(−0·91)	(0·13)		
	150·18	133·48	128·21	121·37	136·94		
F	(−2·12)	(1·48)	(2·61)	(−1·63)	(−0·56)		
	136·53	139·86	123·21	122·24	137·92		
Cl[b]	(−3·22)	(−6·15)	(−1·29)	(−0·92)	(−1·11)		
	129·32	141·43	123·54	121·83	138·73		
Br	(−1·11)	(−8·36)	(−0·72)	(−1·67)	(−0·75)		
	152·69	130·82	120·78	117·03	134·67	50·62	
OMe[b]	(0·45)	(−1·65)	(−3·52)	(−0·51)	(−1·40)		
	150·80	127·12	122·84	110·23	136·84		
NH_2	(1·60)	(−3·28)	(−1·16)	(−3·67)	(−1·86)		
	151·20	131·24	120·09	114·47	135·00	29·45	
NHMe	(2·40)	(2·24)	(−3·19)	(1·12)	(−2·72)		
	148·49	130·13	120·41	114·11	133·39	140·69	126·69
NHPh[c]	(−4·14)	(−4·39)	(−2·23)	(−0·01)	(−6·54)	118·65	116·69
	152·00	135·18	121·08	118·81	136·94	40·01	
NMe_2[b]	(4·55)	(7·78)	(−1·79)	(6·50)	(−0·13)		
	140·50	150·92	123·48	126·40	136·85	165·94	59·22
COOEt[d]	(4·25)	(4·27)	(0·75)	(−1·45)	(−2·17)	12·99	
	133·10	144·77	122·67	125·36	133·77	168·56	
$CONH_2$	(−4·51)	(0·82)	(−0·44)	(−2·02)	(−3·74)		
	128·85	146·32	124·39	127·21	135·51	107·25	
CN	(6·70)	(−3·49)	(1·60)	(−0·56)	(−4·84)		
NO_2			See ref. 6				
ΔSCS[e]	23·84	19·20	8·12	23·34	5·38		

[a] Differences between observed and calculated chemical shifts are given in in parentheses.
[b] Assignment was ascertained from 2D C–H correlated spectra.
[c] Benzene substituent increments were used for the calculations of chemical shifts.
[d] Increments for the COOMe group were used for the calculations of chemical shifts.
[e] Range of SCSs.

$s = 1 \cdot 270$] for ten points, i.e. R = H, Me, Cl, Br, OMe, NH_2, NHMe, NO_2, CO_2Et and $CONH_2$. This means that the chemical shifts of the *para* carbons in Series **4** are less sensitive to the substituent effect. Moreover, it shows that the strong conjugation of the 4-amino group decreases the substituent effect at position 3 much more than the ring aza atom.

The relationships of chemical shifts for 2-substituted 3-aminopyridines vs those for 2-substituted 3-nitropyridines,[7] indicated by the slope ($A < 0 \cdot 9$), show

Table 2. ^{13}C NMR chemical shifts (experimental and calculated)[a] (δ, ppm) of 4-substituted 3-aminopyridines

R	C-2	C-3	C-4	C-5	C-6	Others	
H			See Table 1				
	136·42	141·41	129·93	124·72	139·48	13·18	
Me	(2·05)	(−4·70)	(−2·55)	(−0·79)	(−2·11)		
	135·83	132·74	152·40	105·11	140·69	54·77	
OMe	(−3·15)	(1·25)	(1·49)	(−5·78)	(−0·61)		
	135·36	130·92	141·65	108·65	139·63		
NH_2	(−3·47)	(−0·50)	(0·31)	(−2·17)	(−0·30)		
	132·46	128·68	141·25	109·41	138·76	27·31	
NHMe	(−5·94)	(−0·62)	(−0·25)	(0·71)	(−0·74)		
	136·68	133·67	136·17	108·86	138·93	141·71	129·18
NHPh[b,c]	(−2·15)	(−0·85)	(−0·27)	(−5·06)	(−1·00)	121·30	119·03
	136·97	136·38	146·54	112·70	140·68	41·96	
NMe_2	(−0·76)	(8·26)	(6·50)	(5·18)	(1·85)		
	136·52	144·69	115·50	122·71	140·52	166·86	60·88
COOEt[d]	(−2·34)	(0·69)	(6·91)	(−0·69)	(0·54)	14·04	
	138·24	142·84	127·07	122·86	141·60	170·32	
$CONH_2$[b]	(−3·99)	(−4·00)	(−4·02)	(−3·38)	(−1·73)		
	134·52	139·79	132·82	116·04	144·66		
NO_2	(−2·11)	(−2·43)	(6·98)	(−5·58)	(6·93)		
ΔSCS[e]	5·76	16·01	36·90	19·61	6·03		

[a–c]See Table 1.

Table 3. ^{13}C NMR chemical shifts (experimental and calculated)[a] (δ, ppm) of 3-substituted 2-aminopyridines

R	C-2	C-3	C-4	C-5	C-6	Others	
	159·84	108·15	137·05	111·97	147·72		
H	(1·62)	(−0·40)	(−0·68)	(−2·05)	(−0·44)		
	156·97	116·26	137·18	113·39	144·59	16·43	
Me	(−2·55)	(−1·29)	(−0·75)	(0·17)	(−1·27)		
	155·08	114·78	136·67	114·17	145·99		
Cl	(−2·84)	(−1·97)	(−0·86)	(−0·55)	(−0·77)		
	155·69	104·31	140·14	114·57	146·73		
Br	(−4·63)	(−1·64)	(−0·49)	(−0·75)	(−0·53)		
	150·22	141·42	115·59	113·12	138·29	63·29	14·49
OEt[b,c]	(4·35)	(1·17)	(3·54)	(−1·21)	(−1·68)		
NH_2			See Table 1				
	147·66	131·85	113·62	112·29	133·62	29·37	
NHMe[b]	(3·07)	(0·22)	(−5·87)	(−1·31)	(−2·61)		
	159·59	106·24	139·91	112·21	153·33	166·84	60·56
COOEt[d]	(1·23)	(−4·12)	(1·38)	(−1·92)	(1·36)	14·11	
	156·01	113·90	137·94	113·76	154·13	165·94	
$CONH_2$	(−4·91)	(−0·65)	(−1·09)	(−1·56)	(7·47)		
NO_2			See Ref. 6				
ΔSCS[e]	12·18	35·68	26·52	4·34	21·43		

[a,b,d,e]See Table 1.
[c]Increments for OMe were used for the calculations of chemical shifts.

that the 3-amino group reduces the sensitivity of all carbon atoms to the 2-substituent relative to the 3-nitro group. The best linear dependence was found for the *para* carbon 5 [$A = 0{\cdot}86$ ($\pm 0{\cdot}07$), $r = 0{\cdot}987$, $s = 1{\cdot}134$] for 11 points, i.e. R = H, Me, F, CL, Br, OMe, NHMe, $CONH_2$, CO_2Et, CN and NO_2. A similar analysis of the SCSs for aminopyridines (Series **3**) vs those of the corresponding nitro derivatives shows that chemical shifts of the *ipso* carbon 3 are sensitive to the same extent to both nitro and amino moieties. The regression results are as follows: $A = 1{\cdot}02$ ($\pm 0{\cdot}04$), $r = 0{\cdot}985$, $s = 1{\cdot}556$ for $n = 10$ (see above).

As described,[12] the pyridine ring is considered to be a π-deficient system Electron-donor groups, such as amino, should noticeably influence such a property. Moreover, the various posibilities of conjugation of the 2-, 3- and 4-amino moieties may differentiate the withdrawing character of the ring nitrogen atom. A quantitative measure, $^{\pi}\Delta$,[12] for expressing the π-deficiency and π-excess of the compounds investigated can be developed on the basis of correlations of the chemical shifts for substituted aminopyridines vs those for monosubstituted benzenes,[10] i.e. Lynch's approach.[13] Such a regression shows by its slope (Table 5) for the *ipso* carbon that Series **1** can be considered as π-deficient ($^{\pi}\Delta = 0{\cdot}54$), whereas Series **2**–**4** as weakly π-excess ($^{\pi}\Delta = 1{\cdot}09$, $1{\cdot}12$ and $1{\cdot}14$ for Series **2**, **3** and **4**, respectively). It seems that the π-excess of Series **2** is attributable either to a strong through-resonance effect of the substituent in position 4 or to conjugation of the 3-amino group. In Series **3** and **4** the ring nitrogen atom, which is located quasi-*meta* to the *ipso* carbon 3, does not strongly transmit its electron-withdrawing effect and the π-excess in both cases can be attributed to a strong conjugation of the amino group in positions 2 and 4.[3]

These considerations can be supported by the net electronic charges of the ring aza atom, $q_{N(1)}$,[14] which indicates that amino groups occupying positions 2 and 4 are more strongly conjugated with the ring than that in position 3. However, the net electronic charges are not adequate to predict the relative basicities, since the $q_{N(1)}$ sequence is different to the pK_a values of 2-, 3- and 4-aminopyridines.[3,14] Considering the thermodynamic equilibrium of the protonation and STO-3G *ab initio* calculations, it was suggested[14] that the ring nitrogen atom is the first protonation site of aminopyridines no matter where the amino group is positioned. It was

Table 4. ^{13}C NMR chemical shifts (experimental and calculated)[a] (δ ppm) of 3-substituted 4-aminopyridones

R	C-2	C-3	C-4	C-5	C-6	Others	
	148·84	108·49	153·84	108·49	148·84		
H	(−1·89)	(−1·43)	(−1·70)	(−1·43)	(−1·89)		
	148·53	113·46	151·22	107·61	146·48	12·96	
Me[b]	(−3·50)	(−3·46)	(−4·52)	(−1·51)	(−1·95)		
	148·52	122·08	151·01	109·08	147·54	21·22	12·46
Et[b]	(−1·81)	(−3·34)	(−3·93)	(−0·44)	(−0·49)		
	140·95	141·32	138·84	108·15	148·47		
F	(−1·75)	(−4·68)	(−3·46)	(−2·55)	(1·67)		
	148·26	116·34	149·58	109·58	147·43		
Cl[b]	(−2·17)	(−1·78)	(−5·76)	(−1·04)	(−1·90)		
	152·07	106·73	150·35	109·74	148·19		
Br	(−1·76)	(−0·59)	(−8·09)	(−1·38)	(−1·64)		
	140·15	143·23	136·75	108·75	145·11	48·34	
OMe	(1·77)	(1·61)	(−3·11)	(1·48)	(2·57)		
NH_2			See Table 2				
	132·53	130·17	141·89	107·69	139·38	30·07	
NHMe	(−4·57)	(−2·83)	(4·59)	(−2·81)	(0·59)		
	146·10	123·16	148·65	108·64	145·21	144·79	128·19
NHPh[b,c]	(5·07)	(−1·46)	(3·81)	(−2·18)	(4·98)	117·65	113·58
	140·56	135·72	147·81	108·69	145·13	43·03	
NMe_2	(4·95)	(3·44)	(9·85)	(−0·79)	(7·13)		
	149·78	109·15	154·17	109·90	151·20	164·20	58·74
COOEt[b,d]	(−1·09)	(−2·58)	(−2·17)	(−0·13)	(−3·32)	13·98	
	147·84	114·47	155·04	109·77	151·54	163·45	
$CONH_2$[b]	(−5·66)	(−1·43)	(−1·56)	(−0·33)	(2·34)		
NO_2			See Ref. 6				
ΔSCS[e]	18·54	36·50	18·29	5·13	12·01		

[a–e]See Table 1.

Table 5. Correlations[a] between the ^{13}C NMR chemical shifts for substituted aminopyridines and those for monosubstituted benzenes

Series	Carbon	A	Chemical shift (δ, ppm), R = H Exp.	Calc.	n	r	s
1	C-2	0·54	136·77	136·25	14	0·928	2·386
	C-3	0·79	142·99	142·61	14	0·864	3·660
	C-5	0·87	123·52	123·86	14[b]	0·916	2·541
2	C-3	0·87	142·99	142·92	9[c]	0·987	1·072
	C-4	1·09	121·19	120·71	10	0·937	2·154
	C-5	0·88	123·52	122·14	10	0·938	2·091
3	C-2	0·50	159·84	157·28	10	0·899	1·872
	C-3	1·12	108·15	108·11	10	0·987	1·231
	C-4	1·35	137·05	137·51	10	0·980	1·691
	C-6	1·22	147·72	148·05	10	0·996	0·759
4	C-2	0·71	148·84	148·96	14[d]	0·909	2·503
	C-3	1·14	108·49	109·49	14	0·980	1·524
	C-4	0·65	153·84	151·71	14	0·810	3·588
	C-6	0·56	148·84	148·78	14	0·918	1·580

[a] A, slope; n, number of points; r, correlation coefficient; s, standard deviation.
[b] When NH_2, NMe_2 and NO_2 are rejected, $A = 0·78$, $r = 0·988$, $s = 0·741$, $n = 11$.
[c] When NMe_2 is included, $r = 0·736$, $s = 4·079$, $n = 10$.
[d] When NH_2 and NMe_2 are omitted, $A = 0·54$, $r = 0·987$, $s = 1·025$, $n = 12$.

pointed out that neither basicity nor reactivity is related to the charge densities on nitrogens since those of the amino moieties bear greater negative charge than that pyridine ring. Hence one would consider that the n-orbital localization is a determining factor since the lone pair of the ring nitrogen is much more localized than that of the amino function which is conjugated with the π system. The most localized lone pair at the ring nitrogen corresponds to the most basic aminopyridine. The basicity of derivatives in Series **4** was also observed to be greater than that of those in Series **1**–**3**.[3]

Although the linear relationships (the Lynch correlation) of the chemical shifts for the compounds studied vs those for monosubstituted benzenes and pyridines[7,10] (Tables 5 and 6) are far from perfect representations, they make it possible to conclude that the SCSs are controlled by factors other than substituent electronic effects. The proximity effect occurring between the substituent and/or the ring nitrogen atom is strongly evident,[1-3,7] and groups such as NH_2, NMe_2 and NO_2 do not follow the correlation lines. The main reasons for their deviations have been discussed previously.[3,7,9] Since short-range forces prevail, classical field/inductive and resonance contributions can be considered only for a narrow set of substituents. The similar slopes of both types of correlations for Series **3** and **4** (compare Tables 5 and 6) indicate that the influence of the ring nitrogen atom is not as important when the substitutent occupies position 3 and the amino group position 2 or 4. One could assume that the ring nitrogen atom (repulsion of its lone pair) strongly affects the SCSs of *ipso* carbon 2 in Series **1**. Moreover, the breakdown of the Lynch correlations observed for the chemical shifts of carbon atoms attached to the fixed amino group supports a strong conjugation of its lone electron pair with the pyridine system.[3,14]

Correlations of reasonable quality were obtained for the chemical shifts of *para* carbons to the substituent with σ_p^+ parameters[15] when the same points as in Lynch' s analysis were omitted. For carbon 5 (Series **1**) the results were $A = 5·93$ ($\pm 0·59$), intercept $C = 122·50$ ($\pm 0·41$), $r = 0·986$, $s = 1·014$ ($n = 11$; NO_2, NH_2, and NMe_2 were omitted) and for carbon 6 the results were $A = 8·68$ ($\pm 0·81$), $C = 147·50$ ($\pm 0·66$), $r = 0·976$, $s = 1·280$ ($n = 10$) for Series **3** and $A = 4·79$ ($\pm 0·45$), $C = 148·40$ ($\pm 0·39$), $r = 0·959$, $s = 1·303$ ($n = 14$, NMe_2 was excluded) for Series **4**. The slopes of the correlations suggest that different substituent effects are operating in the particular series, and that both the variable position of the ring nitrogen atom and the fixed amino group have important effects.

In general, the dual substituent parameter (DSP) treatment[2,16] allows one to understand SCSs and their relation to electron densities better and also to predict unknown SCSs values and to determine new substituent parameters. As seen in Table 7, the chemical shifts of the *para* positions to the substituent are well fitted to the DSP approach. It is possible to verify that this equation explains more than 95% of the observed variation in the chemical shifts. Thus, they are mainly controlled by electronic (inductive/field and resonance) effects. The better correlations against σ_R^- than σ_R^0 con-

stants confirm the importance of conjugation of the fixed amino group in positions 2 and 4 (Series 3 and 4). Although the results of the DSP analysis are not statistically more significant than those obtained by the single substituent parameter treatment (see above), some interesting conclusions result from such data.

The data in Table 7 show markedly that the chemical shifts in Series **1** are less sensitive to resonance effects than those in Series **3** and **4**. Moreover, the DSP analysis for Series **1** indicates a smaller dependence on the delocalized effect than in monosubstituted benzenes ($\rho_I = 4{\cdot}54$ and $\rho_R^0 = 21{\cdot}5$),[17] although the ratio $\lambda = \rho_I/\rho_R^0$ is changed.[16] For other series such a direct comparison is of little value as different scales σ_R were used. However, the order **1** < **3** < **4** < PhR, which express the λ value, reflects a strong increase in the relevance of resonance interactions in monosubstituted benzenes. Nevertheless, we would suggest that in the series under study, the variable substituent is not a strongly cross-interacting group and its effect is modified by both the ring nitrogen atom and the actual position of the fixed amino group. There is also an implication that non-additivity is caused.

It should be mentioned that combinations of the substituent parameters used in the DSP analysis are the same as those for the ^{1}H NMR chemical shifts of the appropriate *para* hydrogen atoms.[3e] It means that both carbon and proton chemical shifts may be controlled by similar effects. The sensitivity of proton and carbon chemical shifts to the influences of the substituents and the ring nitrogen atom are comparable but not equivalent, since the distances of a proton and a carbon atom at the same ring position from the reaction 'probe' are different.

Table 6. Correlations[a] between the ^{13}C NMR chemical shifts for substituted aminopyridines and those for monosubstituted pyridines

			Chemical shift (δ, ppm), R = H				
Series[a]	Carbon	*A*	Exp.	Calc.	*n*	*r*	*s*
1 vs 2-R	C-2	0·90	136·77	138·55	13	0·907	3·849
	C-3	0·70	142·99	142·33	13	0·852	3·776
	C-5	0·92	123·52	123·07	13[b]	0·917	1·753
2 vs 4-R	C-3	0·70	142·99	142·73	10[c]	0·886	2·798
	C-4	1·09	121·19	120·60	10	0·927	2·377
	C-5	0·93	123·52	122·51	10	0·954	2·053
3 vs 3-R	C-2	0·54	159·84	156·51	10	0·874	2·071
	C-3	1·16	108·15	107·85	10	0·979	1·420
	C-4	1·24	137·05	137·17	10	0·984	1·897
	C-6	1·22	147·72	148·36	10	0·991	1·038
4 vs 3-R	C-2	0·78	148·84	148·43	13	0·890	2·848
	C-3	1·12	108·49	108·98	13	0·983	1·434
	C-4	0·62	153·84	151·45	13	0·936	2·064
	C-6	0·60	148·84	150·17	13[d]	0·898	1·808

[a] See Table 5; 2-, 3- and 4-R mean 2-, 3- and 4-substituted pyridines, respectively.
[b] When NH_2, NMe_2 and NO_2 are rejected, $A = 0{\cdot}85$, $r = 0{\cdot}992$, $s = 0{\cdot}555$, $n = 10$.
[c] When NMe_2 is not included, $A = 0{\cdot}86$, $r = 0{\cdot}966$, $s = 1{\cdot}654$, $n = 9$.
[d] When NMe_2 is omitted, $A = 0{\cdot}71$, $r = 0{\cdot}976$, $s = 1{\cdot}058$, $n = 12$.

Table 7. DSP correlations[a] of the chemical shifts for the *para* carbon atoms in substituted aminopyridines

Series	Carbon	Parameters[b]	$\rho_{I(F)}$	ρ_R	*C*	λ	*r*	*s*	*F*	*n*
1	C-5	σ_I, σ_R^0	8.12	17.27	122.20	2.1	0.973	1.256	159	11[c]
3	C-6	$\sigma_F, \sigma_{\bar{R}}$	7.36	19.37	148.11	2.6	0.992	0.918	486	10
4	C-6	$\sigma_I, \sigma_{\bar{R}}$	2.93	10.33	149.04	3.5	0.978	0.924	193	12[d]

[a] $\rho_{I(F)}$ and ρ_R are the correlation parameters.
[b] σ_I, σ_F, σ_R^0 and $\sigma_{\bar{R}}$ were taken from Refs 15 and 26. *C*, intercept; *F*, test for significance of correlation; for *r*, *s* and *n*, see Table 5.
[c] NMe_2 and NH_2 omitted, NHPh not included (σ_R^0 not available).
[d] NMe_2 and NH_2 excluded.

It seems that the substituent effect for the *ipso* SCSs is evidently neither electronic nor steric in character. Thus, almost equal SCSs for R = F, OR, NHX and NMe_2 are observed. Moreover, the NO_2 moiety exerts a large downfield shift in Series **3** and **4**, although the effect attributed to the hydrogen bonding is expected to be the same in all series.[7] Thus, extensive statistical investigations were carried out on the chemical shifts of *ipso* carbon atoms using different models and scales,[2,18] including electronegativities.[19] Although the result of correlations depends strongly on the choice of substituent parameters,[2] in general correlations of poor quality were obtained. As assumed, there is no relationship to steric effects, either alone or combined with DSP.[2,16,20] The only satisfactory results appeared with the extended DSP equation including Reynolds' so-called non-electronic short-range factor for the *ipso* position, *I*[7,9,21] (see Table 8). Moreover, they prove that the same field/inductive and resonance parameters can estimate the contributions of both localized and delocalized effects in the *ipso* and *para* positions (compare Tables 7 and 8). According to Ehrenson *et al.*,[22] the set of substituents H, Me, F, Cl, Br, OMe, NH_2, NMe_2, NO_2 and CO_2Et for Series **1** and **4** (in Series **1** CN is also included) should give satisfactory statistical evidence. However, the large standard deviations seem to indicate non-electronic competitions other than predicted by Reynolds' factors.

The sensitivity of the *ortho* carbon atoms to the influence of substituents is not completely clear either. Although the chemical shifts of both *ortho* carbons in Series **3** correlate reasonably well with the DSP including Reynolds' factor for the *ortho* position, *O*,[7,9,21] it seems that correlations are overparametrized and σ_I constants for carbon 4 and σ_X for carbon 2 appear superfluous (see Table 8).[23,24] Unfortunately, the two-parameter approach produces much worse results. Moreover, it should be mentioned that the *ortho* carbon chemical shifts in Series **1** and **4** do not fit such an extended DSP approach ($r < 0{\cdot}80$) and, further, inexplicable deviations appear for particular substituents. On the other hand, it is not easy to conclude why only the *ortho* SCSs in Series **3** follow such an analysis. Moreover, the question remains of whether the reasonably good fits for the chemical shifts of the *ortho* carbon atoms in the case of ortho-substituted nitrobenzenes[9] and 2-substituted 3-nitropyridines[7] to the extended DSP equation including Reynolds' factors are of accidental character or are due to properties of the aromatic system with the nitro group present.[24] The above analysis for Series **2** was limited to only six points and the results are not considered here.

More satisfactory correlation results, based on the *r* value, for the *ortho* carbon chemical shifts were obtained using Charton's LDS equation (the steric term ν is included, Table 9).[2,16,20] The best fits were found when the $\sigma_{\bar{R}}$ constants as σ_D parameters were used. In the case of planar π-bonded groups, i.e. R = CO_2Et, $CONH_2$ and NO_2, both the $\sigma_{\bar{R}}$ and ν values were for their planar conformation.[2,3,16,20] Variable signs and magnitudes of the regression coefficients in the LDS approach, i.e. *L*, *D* and *S*, seem to express substituent and fixed amino group effects due to their different positions in the ring. Deviations are observed for similar groups as in the Lynch analysis. The largest values were found for OMe, NH_2, NHPh, NMe_2, NO_2 and halogens. A comparison of the experimental chemical shifts and those calculated from the appropriate regression shows that, in general, those calculated for R = NO_2, NH_2 and OMe are much higher than the experimental values and those for halogens and NMe_2 are much lower. This supports the conclusion that the main reasons for the deviations observed in the correlation analysis of reactivity parameters[3] and ^{13}C NMR chemical shifts are similar.

The correlation results for the chemical shifts of *meta* positions with regard to Lynch plots and multiple substituent parameter treatments were of poor quality

Table 8. DSP extended correlations[a] of the chemical shifts for *ipso* and *ortho* carbon atoms in substituted aminopyridines

Series	Carbon	Parameters[b]	$\rho_{I(F)}$	ρ_R	ρ_X	*C*	*r*	*s*	*F*	*n*
1[c]	C-2	$\sigma_I, \sigma^0_{\bar{R}}$, I	−6·28	−21·93	0·47	140·21	0·973	2·284	71	11
3[d]	C-3	$\sigma_F, \sigma_{\bar{R}}$, I	18·88	−35·49	1·08	105·96	0·988	2·467	105	8
3[e]	C-2	$\sigma_I, \sigma_{\bar{R}}$, O	−6·87	11·07	0·31	159·10	0·996	1·069	138	8
3[f]	C-4	$\sigma_I, \sigma_{\bar{R}}$, O	−0·50	25·57	1·18	137·14	0·980	2·212	60	8
4[g]	C-3	$\sigma_I, \sigma_{\bar{R}}$, I	10·96	−35·75	0·82	108·62	0·987	2·084	129	10

[a] For $\rho_{I(F)}$, ρ_R, *C*, *r*, *s* and *n*, see Tables 5 and 7; ρ_X is regression parameter.
[b] For σ_I, σ_F, $\sigma^0_{\bar{R}}$ and $\sigma_{\bar{R}}$, see Table 7; *I* and *O* are Reynolds' factors for *ipso* and *ortho* positions, respectively (from Ref. 21).
[c] DSP: $r = 0{\cdot}749$, $s = 6{\cdot}056$ and $F = 12$ ($n = 11$).
[d] DSP: $r = 0{\cdot}603$, $s = 9{\cdot}897$ and $F = 5$ ($n = 8$).
[e] DSP: $r = 0{\cdot}877$, $s = 1{\cdot}885$ and $F = 20$ ($n = 8$).
[f] DSP: $r = 0{\cdot}734$, $s = 6{\cdot}521$ and $F = 7$ ($n = 8$).
[g] DSP: $r = 0{\cdot}768$, $s = 9{\cdot}525$ and $F = 12$ ($n = 10$).

Table 9. LDS correlations[a] of the chemical shifts of the *ortho* carbon atoms in substituted aminopyridines

Series	Carbon	*L*	*D*	*S*	*C*	*r*	*F*	*s*	*n*
1	C-3	−3.52	13.61	1.35	142.58	0.967	43	1.733	10[b]
2	C-3	−9.48	12.48	1.28	142.29	0.953	39	1.851	10
	C-5	−3.76	22.50	−4.85	128.74	0.924	21	3.118	10
3	C-2	−3.87	11.65	−7.55	158.82	0.962	48	1.407	10
	C-4	4.66	29.13	−5.94	140.08	0.926	27	3.067	10
4	C-2	13.99	17.97	−4.66	149.87	0.975	70	1.520	12[c]
	C-4	−8.99	13.87	1.23	153.66	0.964	57	1.827	12[d]

[a] *L*, *D* and *S* are coefficients of the LDS equation for σ_I, $\sigma\bar{R}$ and ν constants, respectively; ν parameters are as those in Ref. 3; for *C*, *r*, *s*, *F* and *n*, see Tables 5 and 7.
[b] Br, NO_2, NHPh and NMe_2 are omitted.
[c] NHPh, NH_2 and NO_2 are excluded.
[d] OMe, NMe_2 and NHPh are rejected.

($r < 0{\cdot}7$), probably because of the relatively small range of SCSs.

The above analysis indicates that the observed chemical shifts are non-additive, and are influenced by a number of factors, the contributions of which are difficult to estimate. The substituent effect is evidently sensitive to the variable positions of both substituent and fixed amino groups. No significant influence of the ring nitrogen atom is observed when the substituent occupies position 3 and the fixed amino group position 2 or 4. The SCSs in *ipso*, *ortho* and *para* positions to the substituent are controlled by different factors. The influence of a given substituent extends to atoms whose position is far away from it. In the *para* position the long-range electronic effects as expressed by the DSP are decisive and the resonance component is most important. Correlations for the *ipso* and *ortho* ^{13}C chemical shifts with a more sophisticated variant represent some improvement but there is a question about the reliability of additional substituent factors. The high standard deviations still suggest the possibility of some other effects of a non-electronic nature controlling the SCSs. However, one would concede that common parameters can estimate the contributions of both localized and delocalized effects in the *ipso* and *para* positions for Series **1**, **3** and **4**. It seems that the proximity of the fixed amino group and the ring nitrogen atom cannot reduce the accidental correlations attributable to either environmental effects or insufficient variation in the substituent electronic effect.

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