CARBON-13 SUBSTITUENT-INDUCED CHEMICAL SHIFTS IN BENZENE DERIVATIVES: SUBSTITUTED ANILINES

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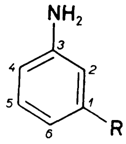
Carbon-13 NMR spectra are reported for 59 *meta*- and *para*-substituted anilines in deuterochloroform or in its mixture with hexadeuterodimethyl sulphoxide. The substituent-induced chemical shifts (SCS) of ring carbon atoms in position 4 correlate well with dual substituent parameters (DSP). In the remaining positions correlations are not satisfactory with any kind of known substituent constants. There is, however, a close resemblance between SCS in the same position of *meta*- and *para*-substituted anilines and even in other series of aromatic compounds.

One approach to understand the substituent-induced chemical shifts (SCS) is to correlate these values with parameters whose physical meaning is in principle known[1,2]. Most popular are correlations with various kinds of σ constants[3], particularly the relation to dual substituents parameters[4] (DSP), σ_I and σ_R (Eq. (*1*)). The applicability of this equation is limited to positions which are not influenced by steric and short-range effects; for this reason most attention has been given to *meta*- and *para*-substituted benzene derivatives (see refs[1,2,5-13] and further literature reviewed in refs[5,6]). In our previous papers we have challenged the DSP approach because it was not the most appropriate in the case of ^{13}C shifts of side-chain carbon atoms, viz. overparametrized on the one hand and insufficiently precise on the other[5,6]. Better results were obtained with principal component analysis (PCA) according to Eq. (*2*). The difference between the two equations is that the parameters of Eq. (*2*) (components B and C) are not known a priori but obtained simultaneously with α, β, γ by an optimization procedure.

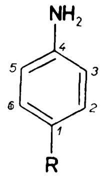
$$\delta = \delta^0 + \varrho_I\sigma_I + \varrho_R\sigma_R \qquad (1)$$

$$\delta_{ij} = \alpha_i + \beta_i B_j + \gamma_i C_j + \ldots \qquad (2)$$

To reach the conclusions above it was necessary to investigate sufficiently large series of compounds with systematically chosen substituents (substituted benzonitriles[5] and methyl benzoates[6]). If the study is extended from side-chain atoms to include ring carbon atoms, the published experimental material[5-9,12-17] has to be completed. In this communication we report ^{13}C NMR chemical shifts of *meta*- and *para*-substituted anilines, *I* and *II*, and we also prove the limitations of the DSP approach and its extensions. PCA will be carried out later on a broader set of data. Measurements on smaller series of substituted anilines have been reported in the literature[7,8,17].



I



II

SCS of ring carbon atoms are known for several extensive series of benzene derivatives[5-9]. Correlation with DSP was found satisfactory[7,8,10-15], though mainly in the position* 4 (once with modified parameters[18]), rarely also in the position 3 (refs[7,8,12,15]). In most cases it was felt necessary to improve the precision with the aid of a more complex equation. One possible refinement, called DSP-NLR (non-linear resonance) Eq. (*3*), was applied[7,8,15] to position 4, or even[8,15] to position 3. Another possibility is to extend the correlation by an additional term[9,14], the specially devised[9] parameters were denoted *I*, *O*, *M* for the positions 1, 2, 3, respectively – the so-called extended DSP treatment (EDSP), Eq. (*4*). Finally a linear combination of two SCS can be correlated with a single constant[16], Eq. (*5*).

$$\delta = \delta^0 + \varrho_I\sigma_I + \varrho_R\sigma_R/(1 - \varepsilon\sigma_R) \qquad (3)$$

$$\delta = \delta^0 + \varrho_I\sigma_I + \varrho_R\sigma_R + \varrho_X X \quad (X = I, O, M) \qquad (4)$$

$$\mathrm{a}(\delta_3 - \delta^0) + \mathrm{b}(\delta_4 - \delta^0) = \sigma_{I,R} \qquad (5)$$

Statistical evidence of the above correlations was generally not conclusive, in some cases the number of experimental data was too limited[12]. Therefore, some authors preferred correlations with calculated charge densities[13] or simple correlations of individual series with each other[10,11,13,19]. In two previous papers of our group[20,21]

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* To avoid any misunderstanding we use the prefixes *meta* and *para* to denote the mutual position of the two substituents in a series of compounds; the position of a given carbon atom in the molecule is denoted by numerals 1—6, beginning with 1 for the atom to which the substituent is bonded (formulae *I* and *II*).

we introduced PCA to this purpose on two SCS sets collected from literature data. In monosubstituted benzenes we treated SCS in all positions together and reduced their number to three components but substituents were clustered into groups[20]. SCS of disubstituted benzenes can to a large extent be modeled from mono derivatives[21]. In conclusion there is little agreement in the literature on this topic and most of the correlations are not well proven statistically. Another complication is that the literature usually does not report on all statistics considered important[26]. Our experimental data give the opportunity to test some of the above relationships in a statistically more significant way.

EXPERIMENTAL

Materials. Substituted anilines were either commercially available or were prepared by well known procedures. 3-Acetoxyaniline, m.p. 57°C, was prepared by catalytic hydrogenation[22] of the nitro derivative on palladium–charcoal. In our opinion it can not be prepared as reported[23], i.e. "from 3-amino-phenol by a standard method". However, the reported ^{13}C NMR spectrum from the same laboratory[8] agrees with ours. Additional six substituted anilines with the substituents $CH_2C_6H_5$, $CH_2OC_6H_5$, and $CH_2SO_2C_6H_5$ were also prepared by catalytic hydrogenation. Only the 3-aminobenzyl phenyl ether has not been sufficiently characterized previously, but its hydrochloride had characteristics (m.p. 143°C) as reported earlier[24].

NMR measurements. ^{13}C NMR spectra were recorded partly in Prague under the conditions as previously reported[5], partly in Umeå on a Bruker AC-P-250 NMR spectrometer, using the same conditions. Both series of measurements were checked on several compounds which were measured twice. The ^{13}C chemical shifts, relative to internal TMS, are given in Tables I and II. Their reproducibility is estimated to ±0·02 p.p.m. SCS given in Table III relate always to the unsubstituted aniline in the same solvent: mostly $CDCl_3$, in some cases $CDCl_3$, with 10% $CD_3.SOCD_3$. Their actual precision was estimated from a comparison with previously published data[7,8] as given in Table IV last line. The agreement of measurements in two laboratories was in this case definitely worse than previously[5]. In addition the distribution of errors shows a strange pattern: all relative shifts in the position *ortho* and *para* to the amino group were in our data more positive (in average by 0·09 p.p.m.) than the literature values[7,8]. We can hardly suggest any reasonable explanation for this deviation except possibly a difference in solvent purity. Nevertheless, the precision is by far not so critical as it was previously in the case of extra-annular carbon atoms[5,6] since SCS in the present case are much larger in magnitude (except for carbon 3).

Incorrect shift assignment may cause some problems. The assignment is unambiguous for symmetrical molecules and for fluoro derivatives where it is aided by the observed coupling constant J(C, F). In the remaining molecules the assignment is based essentially on the number of directly bonded protons and on standard substituent shifts[2]. The last procedure is in fact contradictory: first the assignment is made according to common substituent shifts, where addiivity is assumed, then more exact sutisbtuent shifts are evaluated and their non-additive character is claimed. Even so, this procedure may be reliable in two limiting cases: when the shifts of individual carbon atoms in one molecule are very different, or when some of them are so close that a misassignment is immaterial. Between these two extremes the assignmnent may be doubtful. In important cases we tested the assignment by ^{13}C-^{1}H heterocorrelated 2D-NMR spectra (using HETCOR pulse sequence[25]) and/or by selective proton decoupling in ^{13}C NMR spectra.

In a few instances even these methods were not sufficient and we left the assignment undecided. The chosen alternative was arbitrarily set to those values which gave better correlation and/or closer resemblance to similar compounds. All these cases are marked in Tables I and II. Note that the statistics of the correlations are not affected by such uncertainty since the number of compounds is large and possible differences are relatively small.

The statistical procedures were essentially the same as given previously[5]. Of many correlations carried out only the more important ones are listed in Table IV. In particular when correlations are listed with one kind of σ_R constants only (σ_R^0, σ_R^+, σ_R^-), it means that the fit of the other models was distinctly worse. For the linear regression analyses we employed a statistical procedure as recommended recently[26]. The intercept was fitted freely, giving the same weight to the unsubstituted compounds as to the others but the intercept values were insignificant and are omitted in Table IV. No specific procedure for excluding outliers was used, some individual deviations are mentioned separately in the following discussion.

DISCUSSION

Of the twenty nine substituents investigated, two deserve special attention: aza and $OCOCH_3$. The aza "substituent" showed very distinct deviations[6] even in the plots and correlations not involving any σ constants: substituents of this kind should be investigated separately. The acetoxy group behaves probably normally but the available values of DSP cannot be considered reliable. To obtain comparable results we excluded the two substituents from all calculations, although they are shown in the plots not involving constants σ. On the other hand we have not observed any significant anomalies claimed for some magnetically anisotropic groups like heavier halogens[7,20], trifluoromethyl[20], vinyl[20], formyl[7], phenyl[27], phenoxyl[28]. Substituents containing a phenyl ring in different positions seemed to be a particularly good probe for such effects. For this reason we have inserted into our set the relatively complex substituents $CH_2C_6H_5$, $CH_2OC_6H_5$, and $CH_2SO_2C_6H_5$. Since no deviations were encountered, these groups were treated with the other substituents. No sign of dimerization was observed with *meta* derivatives which have substituents COR or COOR, i.e. no aggregation behaviour similar to that found for hydroxy derivatives[6,29]. The NH_2 group is certainly less effective hydrogen donor than OH. On the other hand individual deviations were observed for substituents OH, SCH_3, and $N(CH_3)_2$ in certain correlations, which will be mentioned where appropriate. In no case was elimination or insertion of one or two substituents of importance for the final conclusion.

There is a fundamental difference in the quality of fit when correlations for the position C-4 are compared with those involving the other positions. The former will be discussed first. The correlations are very similar for the *meta* and *para* substituted derivatives and can be classified as very good based on the correlation coefficient but the standard deviations are still several times larger than the largest possible experimental error (Table IV). Similar results were obtained for more limited series of *meta* (ref.[8]) and *para*-substituted[7] anilines, and also for *para*-

TABLE I

^{13}C NMR chemical shifts of *meta*-substituted anilines in deuterochloroform

Substituent	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
H	129·25	115·08	146·40	115·08	129·25	118·48	—
H^a	129·12	114·93	146·72	114·93	129·12	118·03	—
CH_3	139·12	116·03	146·22	112·37	129·18	119·58	CH_3: 21·40
$CH_2C_6H_5$	142·26	115·69	146·43	112·93	129·27	119·29	CH_2: 41·87, C_6H_5: 141·12(1′); 128·92^b (2′, 6′); 128·35^b (3′, 5′); 125·95 (4′)
$CH_2OC_6H_5$	138·37	114·01	146·49	114·72	129·49	117·61	CH_2: 69·93, C_6H_5: 158·86 (1′); 114·88 (2′, 6′); 129·44 (3′, 5′); 120·86 (4′)
$CH_2SO_2C_6H_5$	129·04	117·22	146·33	115·46	129·39	120·96	CH_2: 62·99, C_6H_5: 138·12 (1′); 128·67^b (2′, 6′); 128·81^b (3′, 5′); 133·60 (4′)
CF_3	131·75	111·38	146·82	118·02	129·78	115·07	CF_3: 124·29
C_6H_5	142·26	113·75^c	146·75	114·02^c	129·58	117·43	C_6H_5: 141·30 (1′); 127·00 (2′, 6′); 128·56 (3′, 5′); 127·12 (4′)
$COCH_3$	138·28	114·04	146·83	119·67	129·44	118·82	C=O: 196·30, CH_3: 26·68
COC_6H_5	137·80^b	115·85	146·57	118·93	129·97	120·49	C=O: 196·91, C_6H_5: 138·66^b (1′); 129·97 (2′, 6′); 128·14 (3′, 5′); 133·23 (4′)
COOH	131·80	116·05	146·58	119·20	129·04	119·67	COOH: 168·69
$COOCH_3$	131·11	115·73	146·71	119·40	129·24	119·53	C=O: 167·35, CH_3: 51·99
$COOCH_2CH_3$	131·42	115·66	146·84	119·36^b	129·18	119·30^b	C=O: 166·90, CH_2: 60·84, CH_3: 14·28

CN	112·89	117·42	147·05	119·21	130·05	121·89	CN: 119·21
F	163·94	102·02	148·57	110·69	130·46	105·05	—
Cl	134·86	114·93	147·66	113·19	130·30	118·45	—
Br	123·01	117·80	147·78	113·59	130·55	121·34	—
I	94·90	123·71	147·70	114·26	130·72	127·41	—
OH	158·15	102·80	147·40	107·06	130·05	106·29	—
OCH_3	160·81	101·20	147·70	108·02	130·11	104·10	OCH_3: 55·06
OCH_2CH_3	160·02	101·53	147·73	107·70	129·97	104·48	CH_2O: 63·09, CH_3: 14·77
$OCOCH_3$	151·69	108·27	147·75	112·66	129·97	111·28	CO: 169·57, CH_3: 21·13
NH_2	147·56	101·96	147·56	105·96	130·17	105·96	—
$N(CH_3)_2$	151·76	99·72	147·36	103·83[c]	129·84	104·44[c]	$N(CH_3)_2$: 40·63
$NHCOCH_3$[a]	139·02	106·72	147·26	111·07	129·66	109·83	CO: 168·54, CH_3: 24·60
NO_2	149·43	109·09	147·60	120·66	129·95	113·16	—
$N{=}NC_6H_5$	153·83	107·51	147·21	117·84	129·82	115·02	C_6H_5: 152·74 (1′); 122·80[b] (2′, 6′); 129·05[b] (3′, 5′); 130·83 (4′)
SCH_3	139·39	113·05[c]	146·87	112·14	129·65	116·79	SCH_3: 15·70
SO_2CH_3	141·34	112·71	147·64	119·66	130·27	116·42	SO_2CH_3: 44·38
SO_2NH_2[a]	144·13	111·72	147·83	117·93	129·51	114·65	—
aza[d]	—	137·48	142·71	121·39	123·71	139·86	—

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[a] A mixture of $CDCl_3$ with CD_3SOCD_3 (10%) was used as solvent; [b] the assignment of signals can be interchanged; [c] the assignment of signals is based on a HETCOR spectrum; [d] 3-aminopyridine.

TABLE II
^{13}C NMR chemical shifts of *para*-substituted anilines in deuterochloroform

Substituent	C-1	C-2,6	C-3,5	C-4	Other carbons
H	118·48	129·25	115·08	146·40	—
H^a	118·03	129·12	114·93	146·72	—
CH_3	127·76	129·76	115·28	143·86	CH_3: 20·44
$CH_2C_6H_5$	131·08	129·68	115·26	144·43	CH_2: 41·03, C_6H_5: 141·88 (1′); 128·74^b (2′, 6′); 128·30^b (3′, 5′); 125·79 (4′)
$CH_2OC_6H_5$	126·90	129·33^b	115·14	146·28	CH_2: 70·07, C_6H_5: 158·97 (1′); 114·94 (2′, 6′); 129·40^b (3′, 5′); 120·74 (4′)
$CH_2SO_2C_6H_5$	117·32	131·84	114·93	147·01	CH_2: 62·47, C_6H_5: 138·15 (1′); 128·68^b (2′, 6′); 128·79^b (3′, 5′); 133·47 (4′)
CF_3	120·25	126·78	114·24	149·49	CF_3: 124·95
C_6H_5	131·52	127·96	115·35	145·83	C_6H_5: 141·14 (1′); 128·64 (2′, 6′); 126·38 (3′, 5′); 126·23 (4′)
$COCH_3$	127·83	130·82	113·73	151·32	C=O: 196·30; CH_3: 26·06
COC_6H_5	127·07	132·90	113·58	151·29	C=O: 195·35, C_6H_5: 138·92 (1′); 129·43 (2′, 6′); 128·05 (3′, 5′); 131·35 (4′)
COOH^a	119·52	131·76	113·66	151·33	COOH: 168·93
$COOCH_3$	119·72	131·60	113·80	150·90	C=O: 167·17, CH_3: 51·57
$COOCH_2CH_3$	120·14	131·58	113·80	150·85	C=O: 166·75, CH_2: 60·30, CH_3: 14·44

CN	100·17	133·78	114·45	150·47	CN: 120·12
F	156·49	115·70	116·10	142·51	—
Cl	123·15	129·12	116·23	144·99	—
Br	110·18	132·00	116·69	145·43	—
I	79·35	137·97	117·32	146·13	—
OH	150·04	116·73[b]	116·11[b]	138·47	—
OCH_3	152·66	114·87	116·42	140·02	OCH_3: 55·75
OCH_2CH_3	151·87	115·56	116·25	139·96	CH_2: 63·90, CH_3: 14·90
$OCOCH_3$	142·86	122·11	115·59	144·25	C=O: 170·04, CH_3: 21·04
NH_2	138·63	116·73	116·73	138·63	—
$N(CH_3)_2$	144·64	115·65[c]	116·62[c]	138·01	$N(CH_3)_2$: 42·12
$NHCOCH_3$[a]	129·88	121·74	115·03	143·14	C=O: 168·33, CH_3: 23·93
NO_2	139·37	126·36	113·47	152·55	—
$N{=}NC_6H_5$	145·57	125·09	114·60	149·60	C_6H_5: 153·01 (1′); 122·33 (2′, 6′); 128·95 (3′, 5′) 129·77 (4′)
SCH_3	125·85[c]	131·15[c]	115·74	145·18	SCH_3: 18·80
SO_2CH_3	128·88	129·45	114·10	151·38	CH_3: 44·99
SO_2NH_2	131·17	128·16	113·82	150·62	—
aza[d]	—	150·31	109·63	152·68	—

[a–c] See Table I; [d] 4-aminopyridine.

TABLE III

Substituent effects in ^{13}C NMR spectra of *meta*- and *para*-substituted anilines

Substituent	*meta*-Substituted anilines						*para*-Substituted anilines			
	C-1	C-2;	C-6	C-3;	C-5	C-4	C-1	C-2,6	C-3,5	C-4
CH_3	9·87	0·95;	1·10	−0·18;	−0·07	−2·71	9·28	0·51	0·20	−2·54
$CH_2C_6H_5$	13·01	0·61;	0·81	0·03;	0·02	−2·15	12·60	0·43	0·18	−1·97
$CH_2OC_6H_5$	9·12	−1·07;	−0·87	0·09;	0·24	−0·36	8·42	0·08	0·06	−0·12
$CH_2SO_2C_6H_5$	−0·21	2·14;	2·48	−0·07;	0·14	0·38	−1·16	2·59	−0·15	0·61
CF_3	2·50	−3·70;	−3·41	0·42;	0·53	2·94	1·77	−2·47	−0·84	3·09
C_6H_5	13·01	−1·33;	−1·05	0·35;	0·33	−1·06	13·04	−1·29	0·27	−0·57
$COCH_3$	9·03	−1·04;	0·34	0·43;	0·19	4·59	9·35	1·57	−1·35	4·92
COC_6H_5	8·55	0·77;	2·01	0·17;	0·72	3·85	8·59	3·65	−1·50	4·89
$COOH^a$	2·55	0·97;	1·19	0·18;	−0·21	4·12	1·49	2·64	−1·27	4·61
$COOCH_3$	1·86	0·65;	1·05	0·31;	−0·01	4·32	1·24	2·35	−1·28	4·50
$COOCH_2CH_3$	2·17	0·58;	0·88	0·44;	−0·07	4·22	1·66	2·33	−1·28	4·45
CN	−16·36	2·34;	3·41	0·65;	0·80	4·13	−18·31	4·53	−0·63	4·07
F	34·69	−13·06;	−13·43	2·17;	1·21	−4·39	38·01	−13·55	1·02	−3·89

Cl	5·61	−0·15; −0·03	1·26; 1·05	−1·89	4·67	−0·13	1·15	−1·41
Br	−6·24	2·72; 2·86	1·38; 1·30	−1·49	−8·30	2·75	1·61	−0·97
I	−34·35	8·63; 8·93	1·30; 1·47	−0·82	−39·13	8·72	2·24	−0·27
OH	28·90	−12·28; −12·19	1·00; 0·80	−8·02	31·56	−12·52	1·03	−7·93
OCH_3	31·56	−13·88; −14·38	1·30; 0·86	−7·06	34·18	−14·38	1·34	−6·38
OCH_2CH_3	30·77	−13·55; −14·00	1·30; 0·72	−7·38	33·39	−13·69	1·17	−6·44
$OCOCH_3$	22·44	−6·81; −7·20	1·35; 0·72	−2·42	24·38	−7·14	0·51	−2·15
NH_2	18·31	−13·12; −12·52	1·16; 0·92	−9·12	20·15	−12·52	1·65	−7·77
$N(CH_3)_2$	22·51	−15·36; −14·04	0·96; 0·59	−11·25	26·16	−13·60	1·54	−8·39
$NHCOCH_3$[a]	9·77	−8·36; −8·65	0·86; 0·41	−4·01	11·85	−7·38	0·10	−3·58
NO_2	20·18	−5·99; −5·32	1·20; 0·70	5·58	20·89	−2·89	−1·61	6·15
$N{=}NC_6H_5$	24·58	−7·57; −3·46	0·81; 0·57	2·76	27·09	−4·16	−0·48	3·20
SCH_3	10·14	−2·03; −1·69	0·47; 0·40	−2·94	7·37	1·90	0·66	−1·22
SO_2CH_3	12·09	−2·37; −2·06	1·24; 1·02	4·58	10·40	0·20	−0·98	4·98
SO_2NH_2[a]	15·01	−3·21; −3·38	1·11; 0·39	3·00	12·69	−1·09	−1·26	4·22
aza[b]	—	22·40; 21·38	−3·69; −5·54	6·31	—	21·06	−5·45	6·28

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[a] Either *para*-derivatives (COOH and $NHCOCH_3$) or *meta*-derivative (SO_2NH_2) were measured in a mixture of $CDCl_3$ with CD_3SOCD_3 (10%) and referenced to aniline in the same solvent; [b] substituent effects obtained from 3- and 4-aminopyridine.

TABLE IV
Correlation of ^{13}C SCS of intraannular carbon atoms in substituted anilines

Correlation	Explanatory variables			Regression coefficients			s^a		R^b
C-1:									
DSP *meta*	σ_I	σ_R^0		-3.29^c	-26.83^c		13·89	(25)	0·440
DSP *para*	σ_I	σ_R^0		-4.10^c	-31.90^c		15·28	(25)	0·469
EDSP *meta*	σ_I	σ_R^0	I	10.06^d	−38·07	0·98	1·66	(11)	0·997
EDSP *para*	σ_I	σ_R^0	I	9.87^d	−43·13	1·09	2·24	(11)	0·995
para vs *meta*	δ_1			1·11			1·14	(26)	0·998
C-2,6:									
DSP *meta* C-2	σ_I	σ_R^{+e}		-6.84^c	8.79^d		4·31	(25)	0·750
C-6	σ_I	σ_R^{+e}		-7.24^c	9.22^d		4·22	(25)	0·771
DSP *para*	σ_I	σ_R^{+e}		-5.43^c	9·84		3·96	(25)	0·812
ESDP *meta* C-2	σ_I	σ_R^0	O	f	19·60	1·00	1·18	(12)	0·988
C-6	σ_I	σ_R^0	O	-3.24^d	21·54	1·00	0·756	(11)	0·996
EDSP *para*	σ_I	σ_R^0	O	f	22·54	0·91	1·02	(12)	0·992
para vs *meta* C-2	$\delta_{2,6}$			0·932			1·28	(26)	0·979
C-6	$\delta_{2,6}$			0·953			1·04	(26)	0·987

C-3,5:									
DSP *meta* C-3	σ_I	σ_R^0		2·49	−1·73		0·245	(25)	0·912
C-5	σ_I	σ_R^0		1·70[d]	−1·07[d]		0·366	(25)	0·698
DSP *para*	σ_I	σ_R^0		[f]	−4·27		0·573	(26)	0·876
DSP-NLR *meta* C-3	σ_I	σ_R^0		2·49	−1·70	(ε −0·04)	0·249	(24)	0·912
C-5	σ_I	σ_R^0		1·79	−1·46	(ε 1·64)	0·368	(24)	0·711
DSP-NLR *para*	σ_I	σ_R^0		0·440	−6·04	(ε 2·12)	0·451	(24)	0·928
EDSP *meta* C-3	σ_I	σ_R^0	*M*	2·51	−2·11	[f]	0·240	(12)	0·934
C-5	σ_I	σ_R^0	*M*	1·42	−1·19	0·612	0·136	(11)	0·969
EDSP *para*	σ_I	σ_R^0	*M*	[f]	−4·16	1·48	0·395	(12)	0·957
meta C-3 vs C-5	δ_3			0·660			0·321	(26)	0·769
para vs *meta* C-3	$\delta_{3,5}$			0·229			0·520	(26)	0·456
C-5	$\delta_{3,5}$			0·206			0·441	(26)	0·477
C-4:									
DSP *meta*	σ_I	σ_R^0		4·93	18·86		0·576	(25)	0·993
DSP *para*	σ_I	σ_R^0		4·95	17·71		0·523	(25)	0·994
DSP-NLR *meta*	σ_I	σ_R^0		4·96	18·00	(ε −0·11)	0·515	(24)	0·995
DSP-NLR *para*	σ_I	σ_R^0		4·93	18·13	(ε 0·07)	0·529	(24)	0·994
para vs *meta*	δ_4			1·04			0·521	(26)	0·994
Differences between laboratories							0·095	(136)	

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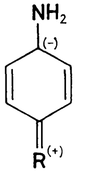
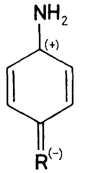
[a] Standard deviation in ppm (in parentheses degrees of freedom); [b] multiple correlation coefficient or absolute value of the simple correlation coefficient; [c] partial correlation coefficient less than 0·5; [d] partial correlation coefficient less than 0·8; [e] correlation slightly better than with σ_R^0; [f] this term not involved in the final correlation since it was insignificant according to the t-test, α 0·05.

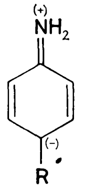
-substituted phenols[14] and triphenyls[15]. The substituent effect is evidently not sensitive to the presence of a fixed functional group neither to its actual position. Although the fit was approximately the same, it was subjectively evaluated by different authors as "excellent"[14], "good precision"[8], or "not inadequate"[7]. Only in the case of *meta*- and *para*-substituted styrenes an "outstanding" fit was claimed[9] ($r = 0{\cdot}9999$) but the statistical procedure employed was in fact not simple regression, but PCA, this means that the values of σ were also optimized.



III



IV



V

The present correlations point to the great importance of mesomeric compared to inductive efects: the ratio of the regression coefficients $\varrho_R/\varrho_I = 3{\cdot}5 - 3{\cdot}8$ is similar as for ^{19}F shifts[30] in the position 4. On the contrary, there is some support that the conjugation does not include the NH_2 group: Firstly, the values of ϱ_R (and also of ϱ_I) do not differ significantly when the constant amino group is in the *meta* or *para* position. This is confirmed by a direct regression of *para* vs *meta* derivatives with a slope insignificantly different from unity (Table IV). Secondly, the correlation with σ_R^- constants, accounting for such conjugation, is not better than with normal constants σ_R^0. A more detailed comparison is accomplished by the DSP-NLR method[7] which can detect even smaller differences in the electron demand. In our case this approach does not yield any improvement: the values of parameter ε are not significantly different from zero, the fit is not improved, and parameters ϱ_I and ϱ_R are not changed. This statement is contrary to that obtained on a smaller data set[7]. We conclude that SCS of the carbon C-4 are controlled by the classical inductive and mesomeric effects which corresond to the conjugation of the substituent with the benzene ring but not with the amino group, as shown for the *para* derivatives in formulas *III* and *IV* for donors and acceptors, respectively. For a successful correlation the conjugation of donors is deciding since the values of σ_R for acceptors are small[4], more exactly they are equal to zero for the majority of acceptors and within their errors[3,31]. Recent theoretical treatments[32,33] consider formula *V* to be most important for *para*-substituted derivatives bearing one donor and one acceptor substituent. As already mentioned the standard deviation still suggests some other effects, possibly of nonelectrostatic nature, controlling the C-4 SCS. These could be revealed in a plot of *meta* and *para* shifts against each other. However, Fig. 1 does not show any systematic deviations, but rather several deviating points, mainly for the donor substituents $N(CH_3)_2$, SCH_3, OH, SO_2NH_2, which are not due either to misassignment or to experimental error. These deviating points remain without explanation: when they are deleted, the standard deviation drops to 0·29 which value may be considered as a limit of attainable accuracy. Plots of either *para* or *meta* SCS against SCS in benzene derivatives[16,34] (always on C-4) yield the same picture.

SCS in the remaining positions, 1, 2, or 3 cannot be correlated with DSP even on an approximate level (Table IV). This fact is most strange for position 3 which has been always considered as sufficiently distant to eliminate proximity effects and has been commonly correlated in one equation together with the position 4 when using the framework of the Hammett equation. In some smaller series, the reported correlations were also unsatisfactory, and as a consequence the discussions[7,8] of constants ϱ are quite meaningless; the reported[7,8] constants ϱ agree only in sign with those of Table IV. In addition some of the latter are not significant statistically. A closer inspection also reveals a significant difference between the *meta* and *para* series. In the former, both C-3 and C-5 exhibit only positive shifts, irrespective of the donor or acceptor character of the substituent. SCS in the position 3 and 5 are similar, showing a certain trend (Table IV and Fig. 2). The only exception is the large negative SCS of the aza substituent (not shown in the figure). On the other hand, C-3,5 SCS in the *para* series are more regular: positive for donors and negative

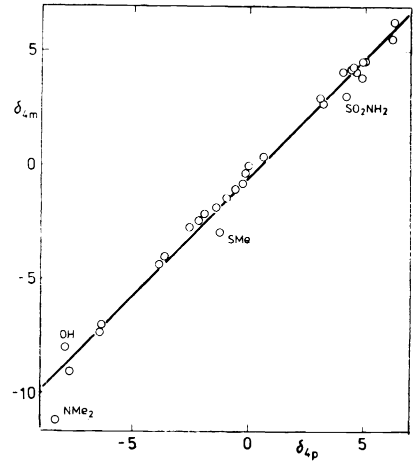


FIG. 1

Linear dependence of SCS of C-4 in *para*-substituted anilines (*x*-axis) vs the same shifts in *meta*-substituted anilines (*y*-axis)

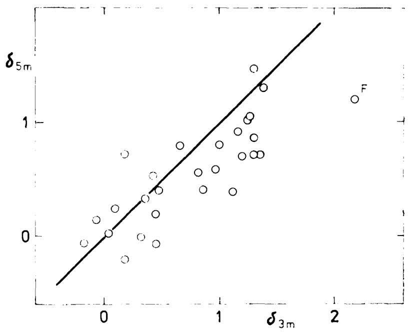


FIG. 2

Plot of SCS in *meta*-substituted anilines in the two similar positions 3 and 5 (*x*-axis and *y*-axis, respectively). The straight line has unity slope for acceptors. The bad fit with DSP is not improved by the DSP-NLR procedure, in contradiction to the previous claim[7], which was based on a shorter series. Lastly we examined the extended DSP treatment[9], Eq. (*4*) with $X = M$. Although the parameters M were determined only from SCS of C-3 (in substituted styrenes[9]), the treatment is not satisfactory and clearly overparametrized (Table IV): either σ_I or M can be omitted. In conclusion, SCS of C-3 do not seem to have any simple physical interpretation. The main problem may be that they are relatively small with respect to SCS in other positions (but they are still sufficiently large compared to the experimental error). A possible explanation could be also connected with the variable conformational equilibrium in the case of axially unsymmetrical substituents in *meta* derivatives. A principal difference in the behaviour of C-3 and C-4 shifts does not agree with the recent theory of Godfrey[35] who treats *meta* and *para* derivatives together by plotting SCS vs the new constants σ_{ST}. In our case the shifts $\delta_{4,p}$ and $\delta_{3,m}$ should be combined, and also $\delta_{4,m}$ and $\delta_{3,p}$. This theory evidently does not apply to ring carbon SCS and it does not apply to extraannular carbon atoms[5,6] either.

SCS in position 2 are larger and somewhat more regular: they may be qualitatively understood in terms of magnetic anisotropy effects[1]. It is thus not surprising that correlations with DSP are very bad but there are important relations between SCS in the individual series. SCS of C-6 in the *meta* series correlate with C-2,6 in the *para* series (Fig. 3), SCS of C-2 in the *meta* series deviate more (not shown). This is understandable since the substituent effect in the latter position is affected also by the adjacent NH_2 group. The effect is evidently neither electrostatic nor steric in character as follows from qualitative observations (almost equal effects of F, OR and NR_2, extreme positive shift by I, opposite effects of CF_3 and CN). As expected there is no relation to the steric parameters, either alone or combined with DSP. The only correlation which appears satisfactory according to the correlation coefficient is the extended DSP treatment with parameters O (Table IV). This is understandable since the parameters O were derived from SCS in the position 2 of substituted styrenes[9]. However, the correlations are overparametrized and constants σ_I appear superfluous. Some insight into the nature of SCS can be gained from a plot of SCS of C-2 against C-1 (Fig. 4). There is an evident general trend with a negative slope and also restricted relationships in particular subsets (always with a negative slope). In this way an alternating substituent effect[36] comes into play as it was often required by theory, particularly from quantum chemical calculations[37,38]. However, this alteration does not proceed further in the benzene backbone: SCS in the position 3 and 4 are controlled by other factors and not related to those in positions 1 and 2.

As expected the C-1 SCS are largest of all and not dependent on DSP: their most striking feature is the controlling effect of the first atom of the substituent. Accordingly, they could be expected to correlate at least roughly with electronegativities. From several scales those denoted σ_α have been obtained by quantum chemical calculations and are available for the largest set of substituents. A plot against the original values[39] (Fig. 5) reveals a rough proportionality for a subset of simple substituents H, SCH_3, CH_3, NR_2, OR, and F, substituents with multiple bonds deviate systematically. The improved values of σ_α, published later[38], seem to be less appropriate. (The negative values for $COCH_3$ and SCH_3 are particularly suspicious.) Best correlations of C-1 SCS are obtained with EDSP including the parameters[9] *I*. Since the later were derived also from C-1 shifts, the correlation does not prove anything more than that these shifts are similar in different series. We can resume that they are controlled directly by the adjacent substituent and are relatively inde-

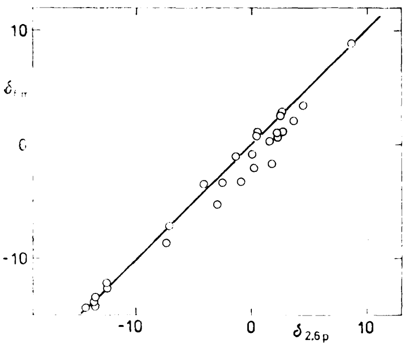


FIG. 3

Plot of SCS of C-2,6 in *para*-substituted anilines (*x*-axis) vs C-6 in *meta*-substituted anilines (*y*-axis). The straight line has unity slope

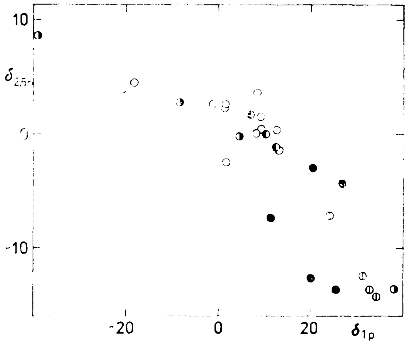


FIG. 4

Plots of SCS of C-1 in *para*-substituted anilines (*x*-axis) vs the shifts of C-2,6 in the same compounds (*y*-axis). ○ C-substituents, ● N-substituents, ⦶ O-substituents, ◐ S-substituents, ◑ halogens

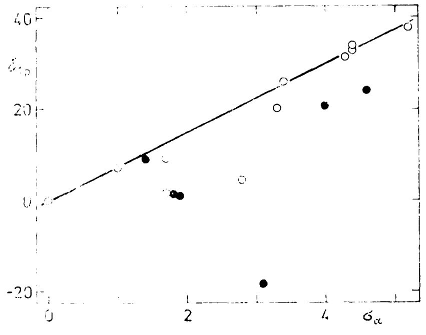


FIG. 5

Plot of C-1 SCS in *para*-substituted anilines vs the electronegativity constants σ_α (ref.[39]). ○ substituents without double bonds, ● substituents with double bonds. The straight line is an estimate for 9 points pendent of the remote parts of the molecule. Nevertheless, the significance of all terms of Eq. (*4*) is questionable even in this case. Similarity of SCS in individual series can be demonstrated more efficiently by a direct correlation of the meta and para series (Table IV) which is still somewhat better than more sophisticated multiple-term correlations.

We are forced to the strange conclusion that SCS in the four different positions of the benzene ring are controlled by four different mechanisms. We can at best concede that the shifts in the positions 1 and 2 have one common controlling factor, but the others are completely different in character: those in the position 4 depend on classical electronic effects while for position 3 there is no obvious rationalization. Except for position 3 there is a close resemblance between individual series of compounds. Our statement is somewhat at variance with the PCA carried out on a larger but less systematical data set which concluded that three factors explain 85% of the total variance[20]. We hope that subsequent PCA of a larger SCS data set will resolve the problem.

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