[Chem. Pharm. Bull. 31(11)4172—4177(1983)]

Electronic Properties of Anticonvulsant Amides. A C-13 Nuclear Magnetic Resonance Study of Phenylacetanilides

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(Received June 23, 1983)

Some twenty phenylacetanilides with *p*- and *m*-substituents in the aniline ring were prepared and their C-13 nuclear magnetic resonance spectra were measured. Substituent chemical shifts (SCS) of the *para*-carbon atom were examined by means of dual substituent parameter (DSP) and DSP-nonlinear resonance (DSP-NLR) equations. Excellent correlations were obtained by DSP analyses. The results indicate that the $-NHCOCH_2Ph$ moiety is a weak electron donor. The chemical shift data and derived correlations are very similar to those obtained for substituted propionanilides.

Keywords——substituent effect; NMR; substituent chemical shift; DSP-analysis; DSP-NLR analysis; electron demand parameter; phenylacetanilide; anticonvulsant activity

Carbon-13 chemical shift measurement is a conventional method for studying the electronic substituent effects in benzene systems. For a series of disubstituted benzenes, *p*-X-C_6H_4-Y (fixed), the ^{13}C SCS (substituent chemical shift) of carbon nuclei *para* to the variable X-substituent can be described by means of the DSP (dual substituent parameter) equation[1] and, in some cases, more accurately by the DSP-NLR (DSP-nonlinear resonance effect) treatment,[2]

$$^{13}C\ SCS = \rho_I\sigma_I + \rho_R\sigma_R^0 \qquad \text{(DSP)}$$

$$^{13}C\ SCS = \rho_I\sigma_I + \rho_R\sigma_R^0/(1-\varepsilon\sigma_R^0) \qquad \text{(DSP-NLR)}$$

where σ_I and σ_R^0 are the inductive and resonance substituent constants of X, respectively, ρ_I and ρ_R are the transmission coefficients, and ε is the electron demand parameter.[2] Three fitting parameters (ρ_I, ρ_R and ε) are determined by the least-squares method. The value of ε in the DSP-NLR correlation has been shown to characterize the "electron demand" exerted by the common Y group on the π-interaction between X and Y.[2] Hence, if the ε value of the Y group in a given system is known, we can expect to estimate the degree of transmission of the substituent effects of X.

In previous work,[3] we applied the DSP and DSP-NLR methods to anticonvulsant-active substituted benzyl *N,N*-dimethyl carbamates (X-C_6H_4–$CH_2OCONMe_2$), for which Hansch analysis[4] showed that the electronic substituent effect was small ($\rho = -0.32$).[5a] As expected, a small ε value (0.06) was obtained from the analysis of C_p-SCS in *p*-substituted derivatives, corresponding to the fact that the active carbamoyl moiety is insulated from direct π-interactions with the aromatic ring by the CH_2 group.

Our continuing study of structure–activity relationships has now been extended to *p*- and *m*-substituted phenylacetanilides (I and II), in which the amide group NHCOR, responsible for anticonvulsant activity, is directly bonded to the aromatic ring. It is expected that, the

potency in systems I and II will be more sensitive to the electronic properties of X than in the case of benzylcarbamates, and indeed, the results so far obtained support this view.[5b] In this work, C-13 nuclear magnetic resonance (^{13}C-NMR) spectra of I and II were measured and SCS of appropriate carbon nuclei were analyzed by means of DSP, DSP-NLR and some other correlations in order to elucidate the transmission of substituent effects and the nature of the $NHCOCH_2Ph$ moiety. For comparison, propionanilides (III and IV) were also studied.

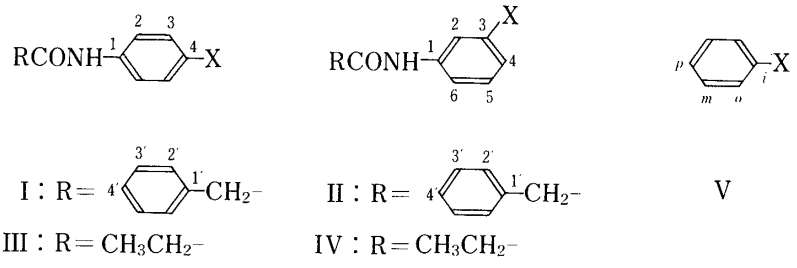

Chart 1

Results and Discussion

The chemical shifts of I—IV are listed in Tables I and II. The signals of the fixed side chains, *i.e.*, $PhCH_2CONH$– and CH_3CH_2CONH–, are readily detected on the basis of their characteristic chemical shifts. The signals of the phenyl ring and those of the aniline ring are clearly distinguished in the case of fluoro compounds (Id and IId), since the ^{13}C signals for the latter are split into doublets arising from ^{13}C–F coupling. For other compounds of I and II, the phenyl carbon nuclei ($PhCH_2CONH$–) were identified based on the assumption that their chemical shifts are little affected by the substituents X. The remaining resonances in the aromatic regions should therefore be assigned to appropriate carbon nuclei of the aniline ring. These assignments were made based on the splitting pattern under off-resonance decoupling conditions and with the aid of the SCS for monosubstituted benzenes.[2]

^{13}C SCS, the chemical shift difference between the substituted species and the parent compound (Ia), for C-1 (*para* to X), C-3 (*ortho* to X) and C-4 (*ipso* to X) of I were plotted against the SCS of corresponding carbon nuclei for monosubstituted benzenes (V); these parameters are designated as SCS_p, SCS_o and SCS_i, respectively. The slopes, together with the correlation coefficients, are listed in Table III. Analogous analyses were carried out for II—IV. The correlations for III and IV should be much the same as those for I and II, since the chemical shift values are very similar in I and III, and in II and IV; only the results for SCS_p are given. The analyses of SCS for carbon nuclei *meta* to X are of limited value since the *meta* increments are hardly influenced by substituents, and thus the results are not included in Table III. Fairly good relationships were obtained between SCS of carbon *para* to X and Hammett's σ_p (Table III).

For *meta*-substituted species II, the coefficients of SCS_i and SCS_p (Eqs. (7) and (8)), 0.99, are very close to unity, confirming that the additivity rule holds for these positions, *i.e.*, for C-3 and C-6. The fact that Hammett correlation (Eq. (9)) is similar to that derived for monosubstituted benzenes (Eq. (14)) supports this consideration. This is not the case for the *para*-substituted species I. The slope of SCS_p, 0.89, which is smaller than unity (Eq. (1)), indicates that the common $PhCH_2CONH$ group reduces the sensitivity of SCS for C-1 to change in the *p*-substituent X. The π-electron interaction between X and NHCOR is responsible for this perturbation.

Hence, in order to estimate the electron demand exerted by the NHCOR moiety, we performed DSP and DSP-NLR analyses for *para* SCS relative to X, *i.e.*, C-1 of I and C-6 of II.

TABLE I. C-13 Chemical Shifts for Phenylacetanilides I—II[a)]

		Aniline ring						$PhCH_2CONH-$						Substituent (X)	
No.	X	C-1	C-2	C-3	C-4	C-5	C-6	C=O	CH_2	C-1′	C-2′,	C-3′[b)]	C-4′		
Ia	H	137.62	119.84	128.93	124.45			169.10	44.83	134.45	129.21,	129.50	127.65		
Ib	OMe	130.82	121.89	114.03	156.47			169.16	44.49	134.71	129.08,	129.46	127.47	OMe	55.44
Ic	Me	135.17	120.06	129.52	134.09[c)]			169.15	44.73	134.67[c)]	129.15,	129.41	127.56	Me	20.86
Id	F	133.59	121.74	115.57	159.45			169.11	44.69	134.32	129.26,	129.51	127.74		
		(^4J=3.2)[d)]	(^3J=7.8)	(^2J=22.2)	(^1J=243.4)										
Ie	Cl	136.20	121.11	128.92	129.48			169.19	44.72	134.17	129.26,	129.48	127.75		
If	Br	136.67	121.33	131.89	117.03			169.06	44.81	134.12	129.32,	129.51	127.81		
Ig	CN	141.61	119.49	133.21	107.34			169.32	44.90	133.68	129.46,	129.46	127.98	CN	118.96
Ih	NO_2	143.48	119.09	124.99	143.56			169.60	44.81	133.60	129.40,	129.43	133.60		
Ii	COMe	142.15	118.98	129.65[c)]	132.93			169.53	44.83	134.04	129.24,	129.44[c)]	127.77	Me	26.43,
														C=O	197.06
IIa	NH_2	138.63	106.42	147.22	111.17	129.62	109.58	168.98	44.99	134.47	129.24,	129.52	127.66		
IIb	OMe	138.88	105.53	160.12	110.31	129.54	111.87	169.13	44.87	134.38	129.20,	129.50	127.65	OMe	55.30
IIc	Me	138.87	120.44	137.52	125.24	128.73	116.89	169.03	44.87	134.48	129.21,	129.49	127.63	Me	21.40
IId	F	139.14	107.29	162.93	111.14	129.97	114.96	169.20	44.80	134.10	129.30,	129.49	127.79		
		(^3J=11.0)	(^2J=26.7)	(^1J=245.7)	(^2J=21.0)	(^3J=9.3)	(^4J=1.6)								
IIe	Cl	138.77	119.93	134.58	124.50	129.91	117.81	169.28	44.76	134.13	129.30,	129.47	127.79		
IIf	Br	138.88	122.70	122.51	127.40	130.20	118.28	169.25	44.73	134.09	129.29,	129.47	127.70		
IIg	CF_3	138.12	116.49	131.35	121.00	129.49	122.85	169.32	44.71	133.96	129.36,	129.49	127.89		
			(^3J=4.2)	(^2J=33.0)	(^3J=4.2)										
IIh	CN	138.45	122.86	112.97	127.97	129.81	123.84	169.37	44.74	133.81	129.40,	129.47	127.84	CN	118.37
IIi	NO_2	138.76	114.56	148.45	119.01	129.80	125.57	169.64	44.68	133.75	129.38,	129.47	127.96		
IIj	COMe	137.65	119.17	138.24	124.51	129.28	124.31	169.48	44.75	134.13	129.28,	129.47	127.77	Me	26.69,
														C=O	197.96

a) In ppm downfield from TMS (solvent $CDCl_3$).
b) Assignments of C-2′ and C-3′ may be interchanged.
c) Assignments interchangeable.
d) Values in parentheses are C–F coupling constants (Hz).

TABLE II. C-13 Chemical Shifts for Propionanilides III—IV[a]

No.	X	C-1	C-2	C-3	C-4	C-5	C-6	C=O	$\underline{C}H_3CH_2-$	$CH_3\underline{C}H_2-$	Substituent (X)
IIIa	H	137.96	119.78	128.95	124.13			172.07	9.67	30.73	
IIIb	OMe	131.08	121.73	114.09	156.30			171.89	9.77	30.54	OMe 55.47
IIIc	Me	135.40	119.88	129.43	133.72			171.94	9.72	30.67	Me 20.83
IIId	F	133.96	121.69	115.58	159.20			172.07	9.68	30.58	
			(^3J=7.8)[b]	(^2J=22.4)	(^1J=242.8)						
IIIe	Cl	136.53	121.05	128.95	129.08			172.15	9.60	30.65	
IIIf	CN	142.02	119.37	133.28	106.90			172.29	9.37	30.83	CN 118.83
IIIg	NO_2	143.74[c]	118.92	125.13	143.53[c]			172.18	9.33	30.90	
IVa	OMe	139.23	105.38	160.15	110.10	129.61	111.77	172.10	9.61	30.79	OMe 55.27
IVb	Me	138.86	120.51	137.92	124.94	128.76	116.89	172.12	9.71	30.74	Me 21.45
IVc	F	139.49	107.27	163.01	110.84	130.03	114.91	172.24	9.56	30.74	
		(^3J=10.6)	(^2J=26.3)	(^1J=244.7)	(^2J=21.5)	(^3J=9.0)	(^4J=1.5)				
IVd	Cl	139.10	119.94	134.59	124.20	129.94	117.75	172.31	9.58	30.74	
IVe	CN	138.91	122.80	112.86	127.50	129.87	123.83	172.49	9.14	30.66	CN 118.57
IVf	NO_2	139.14	114.53	148.50	118.72	129.82	125.54	172.72	9.48	30.66	

a) In ppm downfield from TMS (solvent, $CDCl_3$).
b) Values in parentheses are C–F coupling constants (Hz).
c) Assignments interchangeable.

TABLE III. SCS and Hammett Correlations for Amides I—IV

Series	SCS	Correlation[a]	r[b]	Eq. no.
I	C-1	$SCS_{C-1}=0.89SCS_p+0.14$	0.998	1
	C-3	$SCS_{C-3}=1.00SCS_o+0.30$	0.998	2
	C-4	$SCS_{C-4}=1.02SCS_i-0.64$	0.999	3
	C-1	$SCS_{C-1}=11.32\sigma_p-3.01$	0.947	4
II	C-2	$SCS_{C-2}=0.92SCS_o-0.47$	0.994	5
	C-4	$SCS_{C-4}=0.95SCS_o-0.23$	0.995	6
	C-3	$SCS_{C-3}=0.99SCS_i-0.51$	0.999	7
	C-6	$SCS_{C-6}=0.99SCS_p-0.30$	0.999	8
	C-6	$SCS_{C-6}=12.25\sigma_p-3.75$	0.943	9
III	C-1	$SCS_{C-1}=0.91SCS_p+0.14$	0.999	10
	C-1	$SCS_{C-1}=10.79\sigma_p-3.16$	0.958	11
IV	C-6	$SCS_{C-6}=0.99SCS_p-0.26$	0.999	12
	C-6	$SCS_{C-6}=11.84\sigma_p-3.83$	0.956	13
V	C-4	$SCS_{C-4}=12.47\sigma_p-3.56$	0.952	14

a) $SCS_{i,o,p}$; SCS for monosubstituted benzenes (ref. 2).
b) Correlation coefficient.

TABLE IV. DSP and DSP-NLR Correlations for Amides I—IV

Series	SCS	DSP				DSP-NLR				
		ρ_I	ρ_R	f[a]	SD[b]	ρ_I	ρ_R	ε	f[a]	SD[b]
I	C-1	4.57	19.56	0.06	0.24	4.38	20.27	0.16	0.05	0.21
II	C-6	3.87	21.47	0.03	0.16	3.84	21.69	0.03	0.03	0.16
III	C-1	4.36	19.38	0.02	0.10	4.33	19.54	0.03	0.02	0.10
IV	C-6	3.94	21.69	0.02	0.08	3.97	21.57	−0.02	0.02	0.08

a) f=SD/RMS, where SD is the root mean square of the derivations and RMS is the root mean square of the experimental values; $f \leqq 0.06$ is required for an acceptable fit (see ref. 2).
b) Standard deviation.

The parameters σ_I and σ_R^0 were taken from ref. 1. The derived correlations are summarized in Table IV together with the f values, an index of goodness of fit. Good correlations were obtained by DSP treatments except for series I, for which a small but significant improvement was obtained with the DSP-NLR equation. It is worth noting that ε for *para* derivatives I and III is smaller than expected. Small positive values of ε mean that the NHCOR moiety is an extremely weak electron donor. Though the electron donating property of the NHCOR moiety is weaker than those of NH_2 ($\varepsilon=0.56$)[2] and NMe_2 ($\varepsilon=0.25$)[2] because of the electron-withdrawing carbonyl group, a moderate ε value is expected for NHCOR if SCS_p can be a measure of ε values. Thus, SCS_p for NHCOMe is -5.6, approximately one half of SCS_p for NH_2 (-9.8) or NMe_2 (-11.7).

It is interesting to note that all the results obtained for phenylacetanilides (I and II) are very similar to those for propionanilides (III and IV); this indicates that the SCS values of aromatic carbon nuclei induced by the NHCOR are predominantly determined by the –NHCO– moiety.

In summary, we anticipated that enhanced sensitivity of anticonvulsant potency to the nature of the substituent X (*i.e.*, a greater ρ value) would be associated with a large ε value as

compared with the base of benzyl carbamates. However, the observed small ε values seem to indicate that ε is not a suitable parameter for estimating the magnitude of interactions between X and Y (common substituent) when Y is a moderately interacting group. We are looking for an alternative approach applicable under the above mentioned circumstances.

Experimental

Materials——Phenylacetanilides (I and II) were prepared by treating phenylacetyl chloride with an appropriately substituted aniline by the conventional method. The results of elemental analyses were within $\pm 0.3\%$ of the theoretical values for C, H and N.

^{13}C-NMR Measurements——^{13}C-NMR spectra were recorded at 50.3 MHz on a Varian XL-200 spectrometer in a 10 mm tube at ambient temperature (25 °). A pulse width of 7 μs (corresponding to a flip angle of *ca.* 40 °) was used. The chemical shifts were derermined in 0.1 M $CDCl_3$ solutions (a saturated solution was used for samples of limited solubility) with tetramethylsilane (TMS) as an internal standard. The accuracy of the results is within ± 0.03 ppm.

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