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Predominance of resonance over polar effects on ^{1}H, ^{13}C and ^{15}N NMR substituent chemical shifts in *N*-arylglycines

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ABSTRACT: ^{1}H, ^{13}C and ^{15}N NMR spectra of the ring-substituted *N*-phenylglycines (**1**) and their ethyl esters (**2**) were measured in DMSO-d_6. The chemical shift determinations and assignments are based on modern inverse 2D techniques (HMQC, HMBC). Dependences between chemical shifts and substituent constants show that the substituent effect is well transmitted to some side-chain atoms. There is a good correlation between $\delta_{\mathrm{N^1H}}$ and linear combinations of the inductive, σ_I, and resonance substituent constants, $\sigma_R^{(-)}$, for compounds **2**. Similar results were obtained when the carbonyl carbon chemical shifts in both Series **1** and **2** were related to the substituent constants. Excellent linear dependences were obtained for nitrogen chemical shifts. The correlation coefficient for the linear dependence $\delta_{^{15}\mathrm{N}}$ *vs.* linear combination of inductive and resonance substituent constants is high and it becomes even higher when a correction for the solvent effect is included. In general, the contribution of resonance to chemical shifts is much higher than that of polar effects. The results obtained show $NHCH_2CO_2R$ to be a strong electron donor. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{1}H,^{13}C HMQC; ^{1}H,^{15}N HMBC with *z*-gradient selection; *N*-phenylglycines; substituent effect

INTRODUCTION

NMR parameters, mainly chemical shifts, have been widely applied as a probe of electronic substituent effects.[1–8] The utility of this technique is based on the linear dependence between the measured substituent-induced chemical shifts (SCSs) and the calculated electron densities. To determine the extent of transmission of these effects in aromatic derivatives, ^{13}C and ^{19}F are the most frequently used nuclei. They show a large chemical shift range for a series of the substituents in the ring. In nitrogen-containing molecules, ^{15}N chemical shifts are affected by the substituent present, showing effects similar to those observed for carbon chemical shifts. This also refers to anilines, the chemical shifts of which[9,10] are sensitive to the electronic character of the interacting substituents expressed by the substituent constants. As confirmed by molecular orbital calculations,[11] the upfield and downfield shifts of the ^{15}N signal are directly related to the variation of π electron densities induced by the substituent. Since the SCSs of different lone pair-containing nuclei such as ^{15}N and ^{19}F in aromatic compounds are linearly dependent on each other,[9,10] and ^{19}F chemical shifts are generally accepted to be dominated by the paramagnetic term, it seems reasonable that the same applies to ^{15}N shifts.

Relationships between substituent constants and ^{1}H, ^{13}C, ^{15}N and ^{17}O substituent chemical shifts for ring-substituted aniline derivatives show that contributions of the resonance and inductive effects to $\delta_{^1\mathrm{H}}$ in *para*-substituted anilides are comparable.[12–26]

Dual-substituent parameter (DSP) analysis shows that chemical shift of the carbonyl carbon in *para*-substituted acetanilides is governed largely by the resonance effect of the substituent.[18,23,26,27] It was found that the range of ^{15}N substituent-induced chemical shifts, ΔSCS(^{15}N), in anilines is more than five times that in anilides.[15] The ^{15}N NMR chemical shift for *para*-substituted anilines and anilides was found to be linearly dependent on both inductive and resonance effects of the substituent. The contribution of these two effects to ^{15}N chemical shifts in *para*-substituted anilides is much less, which means that $\delta_{^{15}\mathrm{N}}$ in the spectra of *para*-substituted anilines is more sensitive to the substituent. The contribution of resonance to $\delta_{^{15}\mathrm{N}}$ in anilides ($>80\%$[17,18,20]) significantly predominates such contributions in anilines.[15] The reasonable correlation between ^{15}N chemical shifts and Hammett σ substituent constants[12] shows that ^{15}N chemical shifts in the NMR spectra of acetanilides are governed by conjugation between the lone-pair electrons of the amide nitrogen and π electrons of the benzene ring. On the other hand, strong n_N–$\pi_{C=O}$ resonance interactions in amides may be responsible for the lower ΔSCS(^{15}N) in anilides compared with anilines.[12]

No similar studies have been carried out for *N*-phenylglycines (**1**) and their esters (**2**), which are closely related both to anilines and anilides. From a biochemical (physiological) point of view, such correlation data may be useful when studying non-covalent, i.e. electrostatic, hydrogen bonding, electron donor–acceptor, π–π,

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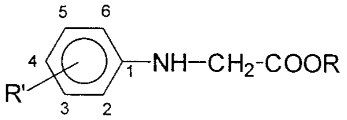

van der Waals and hydrophobic, interactions between high molecular weight assemblies and smaller solute molecules in drug delivery processes[28–31] and also in molecular recognition based on supramolecular complex formation.[32,33] Owing to the presence of a benzene ring in their molecules, *N*-arylglycines are capable of interactions with other aromatic amino acids such as phenylalanine and tryptophan. *N*-Phenylglycines are noteworthy also from another point of view: in spite of conjugative insulation of the CH_2COOH fragment from the Ar—N moiety, their dissociation constants depend on the substituent resonance effect.[34,35] As a consequence, these compounds have been used as standards in the evaluation of unbiased substituent constants.[34–36]

Series **1**, R = H; Series **2**, R = Et

	R′		R′
a	*p*-NO_2	**h**	*p*-Cl
b	*p*-CN	**i**	*p*-OPh
c	*m*-CN	**j**	H
d	*p*-Ac	**k**	*p*-Me
e	*p*-COPh	**l**	*p*-OMe
f	*p*-CO_2Et	**m**	*p*-OH
g	*m*-Cl		

EXPERIMENTAL

All compounds studied were prepared according to reported procedures from the respective ring-substituted anilines and chloroacetic acid or ethyl bromoacetate.[37–41] Some amino acids were obtained from their ethyl esters (hydrolysis). The crude products were purified by repeated recrystallization to gain physical properties consistent with earlier reported values.

The experimental conditions used for recording the NMR spectra were mostly those already published.[42] The ^1H NMR (at 250.130 MHz) and proton composite pulse decoupled (WALTZ-16) ^{13}C NMR spectra (at 62.895 MHz) and *z*-gradient selected $^1H,^{13}C$ HMQC and ^1H,X HMBC (X = ^{13}C and ^{15}N) 2D correlation maps of substituted *N*-phenylglycines and their ethyl esters in DMSO-d_6 (saturated solutions except for ^1H NMR) at 30 °C were recorded with a Bruker Avance DPX250 spectrometer equipped with a 5 mm broadband inverse probehead. The FIDs in ^1H and ^{13}C experiments were apodized by an exponential windowing of digital resolution prior to Fourier transformation in order to improve the signal-to-noise ratio in the NMR spectra.

In ^1H NMR experiments, the conditions were as follows: 0.1 M DMSO-d_6 solution, spectral width 3250 Hz (13 ppm), number of data points 16K, acquisition time 2.5 s, pulse delay 1 s, flip angle 30° and number of scans 4. The ^1H NMR chemical shifts are referenced to the signal of an internal TMS ($\delta = 0.00$ ppm).

In proton composite pulse decoupled (WALTZ-16) ^{13}C experiments, the conditions were as follows: spectral width 14 000 Hz (220 ppm), number of data points 65K, acquisition time 2.3 s, pulse delay 1 s, flip angle 30° and number of scans 100. The ^{13}C NMR chemical shifts are referenced to the signal of an internal TMS ($\delta = 0.00$ ppm).

In 2D $^1H,^{13}C$ HMQC (inv4gs pulse sequence) and 2D $^1H,^{13}C$ HMBC (inv4gslplrnd pulse sequence) experiments with *z*-gradient selection, the conditions were as follows: f_2-axis 2800 Hz/1024 points $\times f_1$-axis 14 000 Hz/1024 points. The delay for transmitting multiple bond correlations was set to 50 ms. The sine-bell window function was used prior to Fourier transformation in both axes. The number of scans was 8 and a composite pulse decoupling (GARP) was used to decouple protons during the pulse sequence. In the *z*-gradient program three sine gradients with relative ratios of 50 : 30 : 40 were used.

In 2D $^1H,^{15}N$ HMBC experiments with *z*-gradient selection (inv4gslplrnd pulse sequence), the spectral parameters were as follows: f_2-axis 2800 Hz/1024 points $\times f_1$-axis 11 200 Hz/1024 points. The delay transmitting multiple bond correlations (*via* geminal and vicinal couplings) was set to 100 ms. The sine-bell window function was used prior to Fourier transformation in both axes. The number of scans was 128. In the *z*-gradient program three sine-bell gradients with relative ratios of 70 : 30 : 50 were used. The ^{15}N NMR chemical shifts are referenced to the signal of an external CH_3NO_2 ($\delta = 0.0$ ppm).

Single- and dual-substituent parameter correlations were obtained using the program Slide Write Plus 2.0. Another program, Winks 4.21, was used for triple-parameter correlations. In all cases the confidence level was 99%. Sources of the substituent constants are as follows: σ, Ref. 36 (except for $\sigma_{p\text{-OH}}$, Ref. 43); σ^-, Ref. 35 (for $\sigma^-_{p\text{-OMe}}$ two different values, i.e. -0.13 or -0.28, were used); σ_I and $\sigma_R{}^-$, Ref. 44; σ_F, σ_R, σ_I and $\Delta\sigma_R$, Ref. 45; and $\sigma°$, Ref. 46.

RESULTS AND DISCUSSION

^1H, ^{13}C and ^{15}N chemical shifts for Series **1** and **2** are compiled in Tables 1–3. The signal of the carboxylic hydrogen is not observed in most spectra of *N*-arylglycines. A wide singlet is usually present for the amino hydrogen of compounds **1**. On the other hand, that signal in the spectra of *N*-arylglycine ethyl esters **2** is often a triplet. It seemed worth relating the δ values of some atoms to the substituent constants. The number of correlation points is given in Tables 4–6 and will not be discussed here. All correlations of $r < 0.9$ were excluded from the tables.

Since the accuracy of its signal position is not reliable (Table 1), the chemical shift of the amino hydrogen in compounds **1** will not be used in correlations. On the other hand, there are linear dependences between δ_{N1H}

Table 1. ^{1}H NMR chemical shifts (δ in ppm from internal TMS) of compounds **1** and **2** measured for 0.1 M solutions in DMSO-d_6

	Series **1**[a]					Series **2**[b]				
Compound	*H*-2 and *H*-6	*H*-3 and *H*-5	N*H*[c]	NC*H*[d]	*H*(R′)	*H*-2 and *H*-6	*H*-3 and *H*-5	N*H*[c]	NC*H*[e]	*H*(R′)
a	6.66	7.99	7.37[f]	3.98[g]	—	6.67	8.00	7.43	4.06	—
b	6.65	7.43	6.75	3.90	—	6.66	7.45	6.91	3.95	—
c	[h]	[h]	6.13	3.88	—	—	—	—	—	—
d	6.62	7.77	6.69	3.93	2.39	6.60	7.73	6.86	4.00	2.41
e	6.66	[i]	6.90	3.94	[i]	—	—	—	—	—
f	6.63	7.75	[j]	3.91	[k]	6.62	7.74	6.42	3.99	[l]
g	[m]	7.00–7.07[n]	6.13	3.88	—	[o]	[p]	6.29	3.92	—
h	6.59	7.97	[q]	3.82	—	6.59	7.10	6.14	3.89	—
i	6.63	6.84	[q]	3.83	[r]	[s]	[t]	5.91	3.90	[t]
j	[u]	[v]	8.70	3.86	—	[w]	[x]	5.92	3.91	—
k	6.53	6.94	8.34	3.82	2.20	6.52	6.93	5.70	3.87	2.19
l	6.36	6.77	[q]	3.62	3.90	6.57	6.75	5.48	3.86	3.66
m	6.45	6.59	[y]	3.72	[y]	—	—	—	—	—

[a] Except for **1e** (very broad singlet at 12.71 ppm), a signal of the carboxylic hydrogen is usually not seen in the spectra of compounds **1**.
[b] Chemical shifts of ethyl hydrogens: 4.13–4.15 ppm (CH_2) and 1.19–1.21 ppm (CH_3).
[c] Wide singlet or regular triplet.
[d] Usually singlet.
[e] Doublet or singlet.
[f] Triplet.
[g] Doublet.
[h] Multiplet at 6.84–6.95 ppm (*H*-2, *H*-4 and *H*-6) and multiplet at 7.16–7.27 ppm (*H*-5).
[i] Multiplet at 7.55–7.64 ppm (*H*-3, *H*-5, *H*-2′, *H*-4′ and *H*-6′) and multiplet at 7.47–7.53 ppm (*H*-3′, *H*-5′).
[j] Overlapped by the signal at 6.63 ppm.
[k] Triplet at 1.26 ppm (CH_3) and quartet at 4.22 ppm (CH_2).
[l] Triplet at 1.27 ppm (CH_3) and quartet at 4.22 ppm (CH_2).
[m] Multiplets at 6.56–6.60 ppm (*H*-2) and 6.48–6.53 ppm (*H*-4 and *H*-6).
[n] Multiplet.
[o] Multiplets at 6.62 ppm (*H*-2) and 6.53 ppm (*H*-6).
[p] Multiplet at 7.04–7.10 ppm.
[q] Signal is not seen in the spectrum.
[r] Doublet at 6.88 ppm (*H*-2′ and *H*-6′), triplet at 6.99 ppm (*H*-4′) and multiplet at 7.28 ppm (*H*-3′ and *H*-5′).
[s] Multiplet at 6.61–6.67 ppm.
[t] Multiplets at 6.83–6.95 ppm (*H*-3, *H*-5, *H*-2′ and *H*-6′) and 7.26–7.34 ppm (*H*-3′ and *H*-5′).
[u] Multiplet at 6.51–6.67 ppm (*H*-2, *H*-4 and *H*-6).
[v] Multiplet at 7.10–7.17 ppm.
[w] Multiplet at 6.58–6.65 ppm (*H*-2, *H*-4 and *H*-6).
[x] Multiplet at 7.08–7.16 ppm.
[y] Wide signal at 8.16 ppm (3H: O*H*, N*H* and CO$_2$*H*).

(range of substituent chemical shift ΔSCS = 1.95 ppm) and $\sigma^{(-)}$ ($r = 0.97$) for Series **2**. Dual-substituent parameter analyses, $\delta_{\mathrm{N^1H}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$, are even more satisfactory ($r = 0.98$).

The substituent chemical shift range for the methylene hydrogen atom in Series **1** is 0.36 ppm. The linear dependence of this shift on both σ and σ^- substituent constants is of low quality (correlation coefficient $r < 0.9$) but dual-substituent parameter treatment (DSP), $\delta_{\mathrm{NC^1H}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$, gives better results ($r \approx 0.92$). The $\delta_{\mathrm{NC^1H}}$ and σ values for Series **2** are not proportional to each other ($r < 0.9$, ΔSCS = 0.20 ppm). The linear dependence of the methylene hydrogen chemical shift, $\delta_{\mathrm{NC^1H}}$, on the σ^- substituent constants is of better quality ($r \approx 0.92$). A fair correlation was obtained for DSP analyses $\delta_{\mathrm{NC^1H}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$ ($r \approx 0.95$). The quality of the $\delta_{\mathrm{N^{13}CH}}$ *vs.* σ and σ^- correlations for Series **1** (ΔSCS = 4.18 ppm) improves from $r < 0.8$ to 0.93 and 0.94 when *m*-Cl and *p*-OMe are rejected, respectively. Unexpectedly, for $\delta_{\mathrm{N^{13}CH}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$ dependences of $r < 0.9$ were obtained. The quality of linear regressions $\delta_{\mathrm{N^{13}CH}}$ *vs.* σ and σ^- for Series **2** ($r = 0.92$, ΔSCS = 1.51 ppm) improves when dual-substituent constants are used ($r \approx 0.96$). All these correlations are at most fair and show that the substituent effect is poorly transmitted to the methylene hydrogen and carbon atoms in the ring-substituted *N*-phenylglycines.

The r values for the dependences of the chemical shift of the carbonyl carbon atom in Series **1** (ΔSCS = 1.74 ppm) on σ, σ^- and $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$ constants are 0.91, 0.98 and 0.99, respectively. When *N*-phenylglycines were used as standards in the evaluation of σ° substituent constants,[34–36] only a fair correlation ($r = 0.95$) was found between $\delta_{\mathrm{^{13}CO}}$ and σ° values. The values of the correlation coefficient for the dependence of the chemical shift of the carbonyl carbon atom for Series **2** on σ,

Table 2. ^{13}C NMR chemical shifts (δ in ppm from internal TMS) of compounds **1** and **2** measured for saturated solutions in DMSO-d_6

Compound	*C*-1	*C*-2 and *C*-6	*C*-3 and *C*-5	*C*-4	N*C*H	*C*O	*C*(R′)	*C*H$_2$ (Et)	*C*H$_3$ (Et)
1a	154.29	111.29	126.06	136.50	44.18	171.48	—	—	—
1b	152.03	112.47	133.57	120.78	44.27	172.12	97.04	—	—
1c	148.97	114.53	119.99	119.74[a]	44.50	172.41	119.72[a]	—	—
		117.34	130.16						
1d	152.60	111.37	130.54	125.83	44.34	172.19	[b]	—	—
1e	152.53	111.20	131.13	124.48	44.08	171.84	[c]	—	—
1f	152.48	111.49	131.09	117.31	44.37	172.24	[d]	—	—
1g	150.00	111.34	133.61	114.78	46.73	172.74	—	—	—
		110.32	130.20						
1h	147.31	113.77	128.73	119.91	44.93	172.63	—	—	—
1i	145.23	113.20	120.98	146.19	45.60	173.00	[e]	—	—
1j	148.47	112.64	129.28	116.82	45.16	173.16	—	—	—
1k	146.19	112.77	129.84	125.28	45.49	173.22	20.38	—	—
1l	143.04	111.27	114.74	150.45	48.26	173.30	57.22	—	—
1m	141.06	113.74	115.84	148.89	45.99	173.20	—	—	—
2a	154.08	111.22	125.89	136.71	44.13	169.99	—	60.73	13.95
2b	151.70	112.17	133.19	120.97	44.21	170.28	96.93	60.54	13.97
2d	152.29	111.07	129.21	125.64	44.09	170.51	[f]	60.42	14.04
2f	152.19	111.23	130.79	117.19	44.17	170.53	[g]	60.43	13.97
2g	149.62	111.49	133.60	115.73	44.44	170.81	—	60.30	14.00
		110.76	130.20						
2h	147.01	113.52	128.46	119.81	44.72	170.92	—	60.31	13.99
2i	144.90	113.14	120.77	146.23	45.14	171.18	[h]	60.22	14.00
2j	148.05	112.15	128.78	116.37	44.80	171.23	—	60.23	14.00
2k	145.77	112.26	129.21	124.80	45.08	171.32	19.94	60.15	13.99
2l	142.22	113.26	114.52	151.26	45.60	171.47	55.21	60.18	14.01

[a] These signals may be interchanged.
[b] 26.01 ppm (CH_3) and 195.52 ppm (*C*O).
[c] 128.18 ppm (*C*-3′ and *C*-5′), 128.81 ppm (*C*-2′ and *C*-6′), 132.25 ppm (*C*-4′) and 138.90 ppm (*C*-1′).
[d] 14.47 ppm (CH_3), 59.83 ppm (CH_2) and 166.14 ppm (*C*O).
[c] 129.75 ppm (*C*-3′ and *C*-5′), 116.68 ppm (*C*-2′ and *C*-6′), 121.94 ppm (*C*-4′) and 158.96 ppm (*C*-1′).
[f] 25.84 ppm (CH_3) and 195.13 ppm (*C*O).
[g] 14.22 ppm (CH_3), 59.55 ppm (CH_2) and 165.81 ppm (*C*O).
[h] 129.55 ppm (*C*-3′ and *C*-5′), 116.54 ppm (*C*-2′ and *C*-6′), 121.77 ppm (*C*-4′) and 158.77 ppm (*C*-1′).

Table 3. ^{15}N NMR chemical shifts [δ in ppm from external CH_3NO_2 ($\delta = 0.0$ ppm)] of compounds **1** and **2** measured for solutions in DMSO-d_6 based on *z*-gradient selected ^{1}H,^{15}N HMBC experiments

Compound	$\delta_{^{15}\mathrm{NH}}$	Compound	$\delta_{^{15}\mathrm{NH}}$
1a	−301.7[a]	**2a**	−303.1[b]
1b	−308.7[c]	**2b**	−309.2[c]
1c	−317.0[c]	—	—
1d	−309.4	**2d**	−310.4
1e	−308.3	—	—
1f	−309.7	**2f**	−311.6
1g	−312.6	**2g**	−318.5
1h	−319.4	**2h**	−320.4
1i	−321.9	**2i**	−323.6
1j	−320.44	**2j**	−321.0
1k	−322.7	**2k**	−321.6
1l	−324.2	**2l**	−326.5
1m	−326.5	—	—

[a,b] Signals of the nitro nitrogens appear at −9.1 and −8.9 ppm, respectively.
[c] Signals of the cyano nitrogens are not seen in the ^{1}H,^{15}N HMBC spectra.

σ^- and $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$ are ≥ 0.99. A much better correlation, as compared with Series **1**, between $\delta_{^{13}\mathrm{CO}}$ and σ° values ($r = 0.99$) was found for Series **2**. The Lower ΔSCS(^{13}CO) value of 1.48 ppm for Series **2**, as compared with Series **1**, is noteworthy.

Correlations $\delta_{^{13}\mathrm{C1}}$ with both σ and σ^- for Series **1** are poor ($r = 0.91$, $\Delta\mathrm{SCS} = 13.23$ ppm). A good linear regression was obtained by plotting $\delta_{^{13}\mathrm{C1}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}{}^-$ and especially *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}$. However, in Series **2** the correlation coefficients are 0.93 and 0.94 for $\delta_{^{13}\mathrm{C1}}$ ($\Delta\mathrm{SCS} = 11.86$ ppm), *vs.* σ and σ° dependences, respectively; DSP analysis gives much better results: $\delta_{^{13}\mathrm{C1}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}$ ($r = 0.99$) and $\delta_{^{13}\mathrm{C1}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}{}^-$ ($r = 0.98$).

The ΔSCS of the nitrogen atom in Series **1** is 24.8 ppm. The correlation coefficient for the dependence $\delta_{^{15}\mathrm{N}}$ *vs.* σ is 0.91 and it increases to 0.96 when *m*-CN is excluded from the regression. The same *r* was obtained for the correlation $\delta_{^{15}\mathrm{N}}$ *vs.* σ^-. Although the DSP analyses, $\delta_{^{15}\mathrm{N}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$, show that there is a very good linear dependence ($r \geqslant 0.99$) for both types of substituent constants (that with σ is slightly better), the

Table 4. Statistical data of the single-substituent parameter correlations $y = \rho x + c$ for Series **1** and **2**[a]

Series	y *vs.* x	n[b]	ρ[c]	c[d]	r[e]
1	$\delta_{^{13}\mathrm{C1}}$ *vs.* σ	13	9.79 ± 1.38	146.24 ± 0.62	0.905
	$\delta_{^{13}\mathrm{C1}}$ *vs.* σ^-	13	7.76 ± 1.05	145.47 ± 0.66	0.913
	$\delta_{\mathrm{N}^{13}\mathrm{CH}}$ *vs.* σ[f]	11	-1.65 ± 0.22	45.30 ± 0.10	0.931
	$\delta_{\mathrm{N}^{13}\mathrm{CH}}$ *vs.* σ^-[f]	11	-1.26 ± 0.15	45.42 ± 0.10	0.941
	$\delta_{^{13}\mathrm{CO}}$ *vs.* σ	13	-1.42 ± 0.19	172.95 ± 0.09	0.911
	$\delta_{^{13}\mathrm{CO}}$ *vs.* σ^-	13	-1.20 ± 0.07	173.09 ± 0.05	0.980
	$\delta_{^{13}\mathrm{CO}}$ *vs.* σ°	11	-1.55 ± 0.17	173.07 ± 0.08	0.950
	$\delta_{^{15}\mathrm{N}}$ *vs.* σ	13	18.34 ± 2.60	-320.35 ± 1.16	0.905
	$\delta_{^{15}\mathrm{N}}$ *vs.* σ[g]	12	20.34 ± 1.79	-320.14 ± 0.77	0.963
	$\delta_{^{15}\mathrm{N}}$ *vs.* σ^-	13	15.33 ± 1.30	-322.14 ± 0.82	0.962
	$\delta_{^{15}\mathrm{N}}$ *vs.* $\sigma_{^{13}\mathrm{C1}}$	13	1.79 ± 0.16	-582.36 ± 24.56	0.956
2	$\delta_{\mathrm{N}^{1}\mathrm{H}}$ *vs.* σ	10	1.65 ± 0.15	5.87 ± 0.06	0.969
	$\delta_{\mathrm{N}^{1}\mathrm{H}}$ *vs.* σ^-	10	1.20 ± 0.10	5.81 ± 0.06	0.976
	$\delta_{\mathrm{N}^{1}\mathrm{H}}$ *vs.* σ^-[h]	10	1.16 ± 0.08	5.84 ± 0.05	0.981
	$\delta_{\mathrm{NC}^{1}\mathrm{H}}$ *vs.* σ^-[h]	10	0.11 ± 0.02	3.89 ± 0.01	0.922
	$\delta_{^{13}\mathrm{C1}}$ *vs.* σ	10	9.96 ± 1.41	146.13 ± 0.61	0.928
	$\delta_{^{13}\mathrm{C1}}$ *vs.* σ^-[h]	10	7.00 ± 0.88	145.97 ± 0.56	0.942
	$\delta_{\mathrm{N}^{13}\mathrm{CH}}$ *vs.* σ	10	-1.34 ± 0.20	44.99 ± 0.08	0.923
	$\delta_{\mathrm{N}^{13}\mathrm{CH}}$ *vs.* σ^-[h]	10	-0.92 ± 0.14	45.01 ± 0.09	0.919
	$\delta_{^{13}\mathrm{CO}}$ *vs.* σ	10	-1.34 ± 0.08	171.18 ± 0.03	0.987
	$\delta_{^{13}\mathrm{CO}}$ *vs.* σ^-[h]	10	-0.94 ± 0.03	171.20 ± 0.02	0.996
	$\delta_{^{13}\mathrm{CO}}$ *vs.* σ°	9	-1.41 ± 0.08	171.22 ± 0.04	0.989
	$\delta_{^{15}\mathrm{N}}$ *vs.* σ	10	19.78 ± 2.57	-321.85 ± 1.11	0.939
	$\delta_{^{15}\mathrm{N}}$ *vs.* σ^-	10	14.92 ± 1.19	-322.87 ± 0.75	0.979
	$\delta_{^{15}\mathrm{N}}$ *vs.* σ^-[h]	10	14.38 ± 1.05	-322.43 ± 0.66	0.979
	$\delta_{^{15}\mathrm{N}}$ *vs.* $\delta_{\mathrm{N}^{1}\mathrm{H}}$	10	12.00 ± 1.06	-392.29 ± 6.70	0.970
	$\delta_{^{15}\mathrm{N}}$ *vs.* $\delta_{^{13}\mathrm{C1}}$	10	1.87 ± 0.21	-595.34 ± 31.13	0.954

[a] If not stated, the value of -0.13 was used for $\sigma^-_{p\text{-OMe}}$.
[b] Number of points.
[c] Slope.
[d] Intercept.
[e] Correlation coefficient.
[f] *p*-OMe and *m*-Cl excluded.
[g] *m*-CN excluded.
[h] $\sigma^-_{p\text{-OMe}} = -0.28$.

correlation $\delta_{^{15}\mathrm{N}}$ *vs.* $\sigma_\mathrm{F} + \sigma_\mathrm{R} + \Delta\sigma_\mathrm{R}$ was found to be excellent ($r = 0.999$). $\Delta\sigma_\mathrm{R}$, i.e. the substituent solvent-assisted resonance parameter (SSAR), is a correction for the influence of the strong hydrogen bond acceptor solvent in compounds bearing certain conjugated π-electron acceptor substituents[13,14,45] and σ_F and σ_R are the gas phase field/inductive and resonance substituent constants, respectively. The ΔSCS of the nitrogen atom in Series **2** (23.4 ppm) is comparable to that in Series **1**. The linear dependence $\delta_{^{15}\mathrm{N}}$ *vs.* σ is not very good ($r = 0.94$) but it improves when σ^- constants are used ($r = 0.98$). DSP analysis $\delta_{^{15}\mathrm{N}}$ *vs.* $\sigma_\mathrm{I} + \sigma_\mathrm{R}^{(-)}$ shows that there is a good linear regression ($r \geq 0.99$). The correlation $\delta_{^{15}\mathrm{N}}$ *vs.* $\sigma_\mathrm{F} + \sigma_\mathrm{R} + \Delta\sigma_\mathrm{R}$ is slightly worse ($r = 0.997$) than that for Series **1**. As can be seen from these results, the SSAR correction for the formation of a solvent–solute complex between *N*-arylglycines and DMSO[45] improves the quality of the linear dependences between their $\delta_{^{15}\mathrm{N}}$ values and substituent constants, especially in Series **1**.

The values of $\lambda = \rho_\mathrm{R}/\rho_\mathrm{I}$ in Tables 5 and 6 show that, in general, the SCSs of ^{13}C-1 and of the side-chain atoms are more dependent on the resonance effect of the substituent than on its inductive/field effect. This is best seen for the chemical shifts of ^{13}C-1 and N^{13}CH. Of course, the substituent resonance effect is transmitted to the side-chain atoms indirectly: it induces a charge on the N atom which subsequently affects the side-chain atoms.

It seemed of interest to check whether the chemical shifts of two different atoms in the molecule change in parallel to each other. The correlation coefficients show this to be the case for $\delta_{^{15}\mathrm{N}}$ *vs.* $\delta_{^{13}\mathrm{C1}}$ in Series **1** and **2** ($r = 0.95$) and for $\delta_{^{15}\mathrm{N}}$ *vs.* $\delta_{\mathrm{N}^{1}\mathrm{H}}$ in Series **2** ($r = 0.97$).

To see the differences in the transmission of the substituent effect in *N*-arylglycines and other related compounds, ^{15}N chemical shifts for Series **1** and **2** were compared with those of the ring-substituted anilines $\mathrm{RC_6H_4NH_2}$[13–16] and anilides $\mathrm{RC_6H_4NHCOR'}$

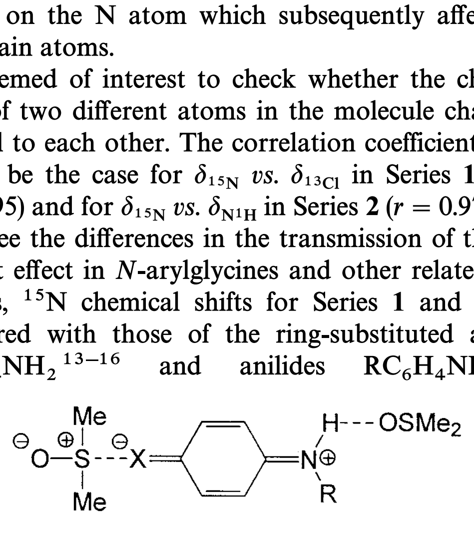

Table 5. Statistical data of the dual-substituent parameter correlations $z = \rho_x x + \rho_y y + c$ (DSP analysis) for Series **1** and **2**

Series	z *vs.* $x + y$	n[a]	ρ_x[b]	ρ_y[b]	c[c]	R[d]	$\lambda = \rho_y/\rho_x$
1	$\delta_{\mathrm{NC^1H}}$ *vs.* $\sigma_I + \sigma_R$	8	0.03 ± 0.08	0.58 ± 0.11	3.84 ± 0.03	0.924	19.33
	$\delta_{\mathrm{NC^1H}}$ *vs.* $\sigma_I + \sigma_R^-$	8	-0.01 ± 0.09	0.29 ± 0.06	3.83 ± 0.03	0.917	29.00
	$\delta_{\mathrm{^{13}C1}}$ *vs.* $\sigma_I + \sigma_R^-$	8	3.96 ± 0.85	20.23 ± 1.23	148.09 ± 0.32	0.994	5.11
	$\delta_{\mathrm{^{13}C1}}$ *vs.* $\sigma_I + \sigma_R^-$	8	2.49 ± 1.26	10.25 ± 0.89	147.74 ± 0.45	0.987	4.12
	$\delta_{\mathrm{^{13}CO}}$ *vs.* $\sigma_I + \sigma_R$	8	-1.63 ± 0.20	-2.27 ± 0.29	173.07 ± 0.08	0.987	1.39
	$\delta_{\mathrm{^{13}CO}}$ *vs.* $\sigma_I + \sigma_R^-$	8	-1.46 ± 0.22	-1.16 ± 0.16	173.11 ± 0.08	0.985	0.79
	$\delta_{\mathrm{^{15}N}}$ *vs.* $\sigma_I + \sigma_R$	8	15.92 ± 1.79	35.05 ± 2.58	-319.86 ± 0.67	0.994	2.20
	$\delta_{\mathrm{^{15}N}}$ *vs.* $\sigma_I + \sigma_R^-$	8	13.35 ± 2.29	17.80 ± 1.62	-320.47 ± 0.81	0.990	1.33
2	$\delta_{\mathrm{N^1H}}$ *vs.* $\sigma_I + \sigma_R$	8	1.45 ± 0.28	2.62 ± 0.41	5.88 ± 0.11	0.975	1.81
	$\delta_{\mathrm{N^1H}}$ *vs.* $\sigma_I + \sigma_R^-$	8	1.24 ± 0.26	1.36 ± 3.23	5.83 ± 0.84	0.982	1.10
	$\delta_{\mathrm{NC^1H}}$ *vs.* $\sigma_I + \sigma_R$	8	0.09 ± 0.04	0.33 ± 0.06	3.91 ± 0.02	0.952	3.67
	$\delta_{\mathrm{NC^1H}}$ *vs.* $\sigma_I + \sigma_R^-$	8	0.07 ± 0.05	0.17 ± 0.03	3.90 ± 0.02	0.943	2.43
	$\delta_{\mathrm{N^{13}CH}}$ *vs.* $\sigma_I + \sigma_R^-$	8	-0.36 ± 0.31	-1.39 ± 0.22	44.85 ± 0.11	0.959	3.86
	$\delta_{\mathrm{N^{13}CH}}$ *vs.* $\sigma_I + \sigma_R$	8	-0.56 ± 0.30	-2.72 ± 0.43	44.80 ± 0.11	0.958	4.86
	$\delta_{\mathrm{^{13}C1}}$ *vs.* $\sigma_I + \sigma_R$	8	4.08 ± 1.06	21.01 ± 1.52	147.66 ± 0.40	0.991	5.15
	$\delta_{\mathrm{^{13}C1}}$ *vs.* $\sigma_I + \sigma_R^-$	8	2.56 ± 1.45	10.64 ± 1.02	147.29 ± 0.52	0.984	4.16
	$\delta_{\mathrm{^{13}CO}}$ *vs.* $\sigma_I + \sigma_R$	8	-1.26 ± 0.09	-2.03 ± 0.14	171.19 ± 0.04	0.996	1.61
	$\delta_{\mathrm{^{13}CO}}$ *vs.* $\sigma_I + \sigma_R^-$	8	-1.10 ± 0.11	-1.04 ± 0.07	171.23 ± 0.04	0.995	0.95
	$\delta_{\mathrm{^{15}N}}$ *vs.* $\sigma_I + \sigma_R$	8	13.73 ± 2.25	36.10 ± 3.23	-320.14 ± 0.84	0.989	2.63
	$\delta_{\mathrm{^{15}N}}$ *vs.* $\sigma_I + \sigma_R^-$	8	11.03 ± 2.35	18.46 ± 1.67	-320.76 ± 0.83	0.989	1.67

[a] Number of points.
[b] Slopes.
[c] Intercept.
[d] Correlation coefficient.

Table 6. Statistical data of the triple-parameter correlations $\delta_{\mathrm{^{15}N}} = \rho_F\sigma_F + \rho_R\sigma_R + \rho_S\Delta\sigma_R + c$ for Series **1** and **2**[a]

Series	n[b]	ρ_F[c]	ρ_R[c]	ρ_S[c]	c[d]	R[e]	$\lambda = \rho_R/\rho_F$
1	8	9.93 ± 1.92	27.93 ± 3.61	31.30 ± 11.59	-320.58 ± 0.55	0.999	2.81
1	9[a]	11.43 ± 2.18	29.41 ± 3.63	31.76 ± 12.90	-320.24 ± 0.61	0.996	2.57
2	8	10.84 ± 1.97	29.27 ± 3.76	26.61 ± 12.02	-320.55 ± 0.55	0.997	2.70

[a] For *p*-OH it was assumed that $\Delta\sigma_R = 0.00$.
[b] Number of points.
[c] Slope.
[d] Intercept.
[e] Correlation coefficient.

(R′ = Me, CF_3, CH_2Ph and Ph).[15,16,24,47] For anilines dissolved in DMSO-d_6 the correlation coefficients are 0.991–0.997 and 0.994–0.997 for Series **1** and **2**, respectively. The correlation coefficients of similar correlations with ^{15}N chemical shifts of anilides (the same solvent) are significantly less satisfactory. Thus, for $\delta_{\mathrm{^{15}N}}$(**1**) *vs.* $\delta_{\mathrm{^{15}N}}$(anilides) $r = 0.780$–0.957 and for $\delta_{\mathrm{^{15}N}}$(**2**) *vs.* $\delta_{\mathrm{^{15}N}}$(anilides) $r = 0.749$–0.983. This shows that compounds **1** and **2** resemble anilines rather than anilides from the point of view of the transmission of the substituent effect to the nitrogen atom. Comparable ΔSCSs for *N*-phenylglycines and anilines, but not for anilides,[15] support this conclusion. Better correlation of $\delta_{\mathrm{^{15}N}}$ *vs.* σ^- than *vs.* σ for compounds **1** and **2** show that *p*-$NHCH_2CO_2R$ is an electron donor substituent. This is consistent with the reported[48] $\sigma_p = -0.68$ value for this group, which seemed unexpectedly high.

The chemical shifts for Series **1** and **2** also deserve to be compared with each other. Good linear dependences were obtained for $\delta_{\mathrm{^{13}C1}}$ ($r = 1.000$), $\delta_{\mathrm{^{13}}}$CO ($r = 0.986$) and $\delta_{\mathrm{^{15}N}}$ ($r = 0.972$). The slopes of these correlations, approximately 1.00 only for ^{15}N and ^{13}C shifts, seem interesting. The chemical shifts of other side-chain atoms for the series studied, i.e. $\delta_{\mathrm{NC^1H}}$ and $\delta_{\mathrm{N^{13}CH}}$, do not change in parallel.

CONCLUSIONS

Analysis of the NMR chemical shifts shows that the substituent effect is poorly transmitted to the methylene hydrogen and carbon atoms in ring-substituted *N*-phenylglycines. On the other hand, the linear dependences between the shift of carbonyl carbon in these compounds on σ^- and $\sigma_I + \sigma_R^{(-)}$ substituent constants and on σ°, σ, σ^- and $\sigma_I + \sigma_R^{(-)}$ constants in their esters are of good quality. DSP analysis shows that the substituent effect is very well transmitted to the *para*-carbon in *N*-phenylglycines and their esters. Excellent correlations were obtained by DSP procedures for ^{15}N chemical shifts, especially when a correction for the influence of the strong hydrogen bond acceptor solvent for π-electron acceptor substituents was included.

The chemical shifts of the *para*-carbon and the side-chain atoms in *N*-phenylglycines and their esters are much more dependent on the resonance effect of the substituent than on its inductive/field effect. $NHCH_2CO_2R$ was found to be a fairly strong electron donor group.

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