^{13}C Nuclear Magnetic Resonance Study of π-Polarization in 3- and 4-Substituted Benzamides and *N*-Chlorobenzamides

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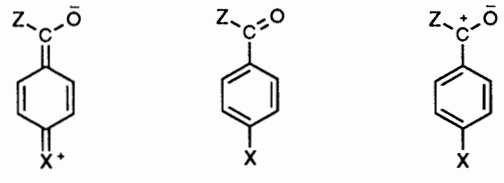
The substituent effect on the carbonyl carbon [C(α)] ^{13}C chemical shift in 3- and 4-substituted benzamides and *N*-chlorobenzamides has been studied in $(CD_3)_2SO$. Chlorine shields the carbonyl carbon. A cross correlation was carried out for C(α) and the carbonyl carbon in *N*-chlorobenzamides is less sensitive to substituents than in the benzamides. The dual substituent parameter method indicated a significant diminution in the π-polarization effect (ρ_I) in *N*-chlorobenzamides compared to benzamides. This is in contrast to other carbonyl systems where ρ_I has been found to be essentially independent of the substituent attached to the carbonyl carbon. It is concluded that π-polarization in benzamide and its derivatives is more sensitive to the substituent attached to the carbonyl carbon than in the other classes of aromatic carbonyl compounds studied to date.

The transmission of substituent effects in aromatic systems continues to be an area of active research. To this end a number of ^{13}C NMR studies have appeared on the influence of ring substituents on the chemical shift of the carbonyl carbon [C(α)] attached to an aromatic ring.[1] Changes in the ^{13}C chemical shift of C(α) can be used to probe how the substituents on the ring interact with the carbonyl group and affect the electron density at C(α).[2] It has been proposed that the chemical shift of C(α) is proportional to the *ab initio* calculated π-electron density at that position.[2] But it has been noted that care should be taken in interpreting variations in ^{13}C chemical shifts solely on the basis of changes in π-electron density.[3]

A carbonyl group adjacent to an aromatic ring containing an electron donating substituent will be a resonance hybrid of the following contributors.



A **B** **C**

Scheme 1

Electron-donating substituents can transfer charge by resonance (**A**) to C(α) and this carbon becomes more shielded. Substituents can inductively effect the π-electron distribution (π-polarization[2,4]) of the carbonyl group. The dipole of the substituent influences whether **B** or **C** will make a greater contribution to the carbonyl resonance hybrid. An electron-withdrawing substituent favours **B** and the carbonyl carbon is shielded. Electron-donating substituents favour **C** and de-shielding is observed. This has been called the 'reverse resonance effect'[1e] since it is contrary to what is observed in **A** (a 'normal resonance effect'). The chemical shift of C(α) will be determined by the relative importance of resonance and inductive effects.

Previous studies on various classes of carbonyl containing aromatic compounds have observed a reverse resonance effect and it has been proposed that π-polarization of the carbonyl bond by the substituent is the most important factor in determining the ^{13}C chemical shift of C(α).[2]

Recently, it was proposed that the π-polarization effect in benzamides was abnormally low.[1q] In order to clarify this point this work examines substituent effects in 3- and 4-substituted benzamides (**1**) and *N*-chlorobenzamides (**2**). It has been reported that, in a series of *N*-chloro-2,6-diarylpiperidin-4-ones, the carbons α to the N–Cl group were deshielded 12–13 ppm.[5] Analogously it would be expected that the nitrogen atom in an *N*-chlorobenzamide (**2**) would be more electronegative than the nitrogen in the corresponding benzamide (**1**). Making the amide nitrogen more electronegative should change the blend of substituent effects and shed further light on π-polarization in benzamides.

The chlorine atom in **2** could influence the ^{13}C chemical shift of C(α) as follows: (i) if the resonance effect becomes more important in **2**, the ^{13}C chemical shift of C(α) would be more sensitive to substituents than in the benzamides (**1**); (ii) the N–Cl dipole could act in the same way as the substituent dipole of an electron-withdrawing ring substituent (**B**) and suppress π-polarization and as a result the ^{13}C chemical shift of C(α) of the *N*-chlorobenzamides would be less sensitive to substituents compared to the benzamides.

In benzamide (**1j**) the torsion angle between the $CONH_2$ group and the ring is *ca.* 25° in the solid state.[6,7] In dioxane a value of 39 ± 2° has been obtained from the molar Kerr constant.[8] *Ab initio*[9] and MM2[10] calculations have given values of *ca.* 30° and 28 ± 2° respectively for this angle. No information is currently available on the torsion angle in *N*-chlorobenzamide (**2j**) or other derivatives. Torsion angles are determined by the interaction of the amide nitrogen substituent(s) and the *ortho* hydrogens/substituents of the ring.[11] The torsion angle in *N*-methylbenzamide has been estimated by NMR[11] to be *ca.* 27° and a linear relationship between the torsion angle and the Taft steric parameter (E_s)[12] was observed. A chlorine atom has a smaller value[12] of E_s than a methyl group and therefore the torsion angle of the two series of compounds in this study would be expected to be comparable.

Results and Discussion

N-Chlorobenzamides (**2**) were prepared by reacting the benzamides (**1**) with *tert*-butyl hypochlorite.[13] Substituents from both ends of the σ scale were used and some 3-substituted

Table 1 ^{13}C Chemical shifts (δ)[a] for 3- and 4-substituted benzamides (**2**) in $(CD_3)_2SO$

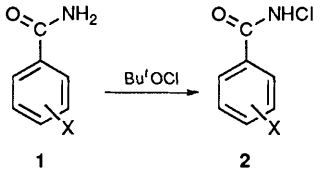
X	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(α)	C(7)
4-NO_2	138.05	129.52	124.14	149.74	124.14	129.52	164.96	
3-NO_2	133.53	122.56	147.86	127.74	130.58	134.14	163.85	
4-CF_3	136.40	129.25	126.52	122.93	126.52	129.25	166.38	132.93
3-Cl	134.00	127.41	133.35	131.91	130.63	126.37	164.40	
3-F	134.27	114.52	161.83	119.04	130.88	123.87	164.51	
4-Cl	130.85	128.70[b]	129.59[b]	137.10	129.59	128.70	164.87	
4-Br	131.22	129.76	131.67	125.96	131.67	129.76	164.97	
4-F	128.59	130.39	115.60	164.24	115.71	130.39	164.77	
H	132.11	127.63	128.61	132.07	128.61	127.63	165.81	
4-CH_3	129.31	127.68	129.13	142.21	129.13	127.68	165.73	21.01
4-OCH_3	124.23	129.64	113.86	162.21	113.86	129.64	165.39	55.43

[a] Chemical shifts (δ) relative to $(CH_3)_4Si$. [b] Assignments interchangeable.

Table 2 Substituent chemical shift (SCS)[a] values[b] (δ) on C(1) and C(α) in benzamides (**1**) and *N*-chlorobenzamides (**2**)

	1		**2**	
X	C(1)	C(α)	C(1)	C(α)
4-NO_2	5.62	−2.21	5.94	−0.85
3-NO_2	1.34	−2.88	1.42	−1.96
4-CF_3	3.73	−1.83	4.29	0.57
3-Cl	1.92	−2.08	1.89	−1.41
3-F	2.43	−1.69	2.16	−1.31
4-Cl	−1.53	−1.66	−1.26	−0.94
4-Br	−0.99	1.50	−0.89	−0.84
4-F	−3.54	−1.19	−3.53	−1.04
H	0.00	0.00	0.00	0.00
4-CH_3	−2.80	−0.06	−2.80	−0.09
4-OCH_3	−7.84	−0.90	−7.88	−0.42
δ-H[c]	134.38	168.59	132.11	165.81

[a] Deshielding indicated by positive value. [b] Relative to $(CH_3)_4Si$. [c] Chemical shift of parent compound (X = H).



1 **2**

a, X = 4-NO_2; **b**, X = 3-NO_2; **c**, X = 4-CF_3; **d**, X = 3-Cl; **e**, X = 3-F; **f**, X = 4-Cl; **g**, X = 4-Br; **h**, X = 4-F; **i**, X = H; **j**, X = 4-CH_3; **k**, X = 4-OCH_3

Scheme 2

compounds were included in this study to examine what happens when direct conjugation with the carbonyl group is not possible. Benzamides and *N*-chlorobenzamides are not very soluble in $CDCl_3$ and, following previous practice [1q,2], ^{13}C NMR spectra were taken in $(CD_3)_2SO$. *N*-Chlorobenzamides (**2**) dechlorinate over a variable period of time in DMSO by what appears to be an autocatalytic process. Spectra were taken immediately after the solution was prepared and, except for *N*-chloro-4-bromobenzamide (**2g**)*, only one carbonyl carbon was observed by ^{13}C NMR. Benzamide (**1**) spectra were redetermined for internal consistency and the chemical shift values for C(1) and C(α) were found to be slightly more shielded (up to 0.7 ppm) than in previous studies.[1q,2] Table 1 contains the assignments for all the carbons in **2** and Table 2 the substituent chemical shifts (SCS) for C(α) and C(1) of **1** and **2**. Substituent chemical shifts (SCS) are defined as follows.

* Different mixtures of **1g** and **2g** were observed by ^{13}C NMR spectra with three samples of *N*-chloro-4-bromobenzamide (**2g**).

Table 3 Results of dual substituent parameter (DSP) analysis of SCS values of compounds **1** and **2**

Compound	ρ_I	ρ_R	ρ_R/ρ_I	n[a]	f
1	−3.11	−0.50	0.16	8	0.16
2	−1.93	−0.18	0.093	6	0.15

[a] Number of data points.

$$SCS = \delta_X - \delta_H$$

Comparison (Table 2) of the C(α) chemical shift for benzamides and *N*-chlorobenzamides with the same substituent indicated that the chlorine atom shielded the carbonyl carbon of all the *N*-chlorobenzamides studied. Relative substituent effects in the two series were examined by plotting C(1) of **1** *vs.* the same carbon in a similarly substituted **2**. An excellent correlation (r = 0.998, n = 11) with a slope of 1.02 ± 0.02 was obtained. A slope of near unity indicated that a similar blend of substituent effects was present in both series of compounds. Therefore any changes in the sensitivity of the ^{13}C chemical shift of C(α) in **2** to substituents can be attributed to the presence of the chlorine atom.

Fig. 1 illustrates a plot of C(α) in **1** *vs.* the same carbon in a similarly substituted **2**. A satisfactory correlation (r = 0.972, n = 9) was obtained with a slope of 0.67. *N*-Chlorobenzamides were less sensitive to substituent effects than were the benzamides. Correlation of *meta* and *para* substituents by the same line indicated no significant direct resonance interaction. To study substituent effects further the C(α) SCS data were analysed using the dual substituent parameter (DSP) equation.[14] With this technique it is possible to separate the SCS into its component inductive and resonance contributions and determine which was affected the most by the presence of the chlorine atom. The magnitude of ρ_I is indicative of the importance of π-polarization in the system.[2]

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R$$

DSP correlations were carried out using various resonance scales[2,14] and no significant differences were noted in the values of ρ_I and ρ_R and f (goodness of fit[14]). Following recent work the $\sigma_{R(BA)}$[1q] resonance scale was used and the data are collected in Table 3. Changes in both the resonance (ρ_R) and inductive (ρ_I) contributions to the SCS of **2** were observed compared to **1**. These results can be contrasted to a previous study in which ρ_I was found to be essentially constant (−2.7 ± 0.3) for a number of *para* substituted carbonyl derivatives but the magnitude of ρ_R depended on the nature of the substituent attached to C(α). The authors of this study concluded that the inductive effects at C(α) are insensitive to

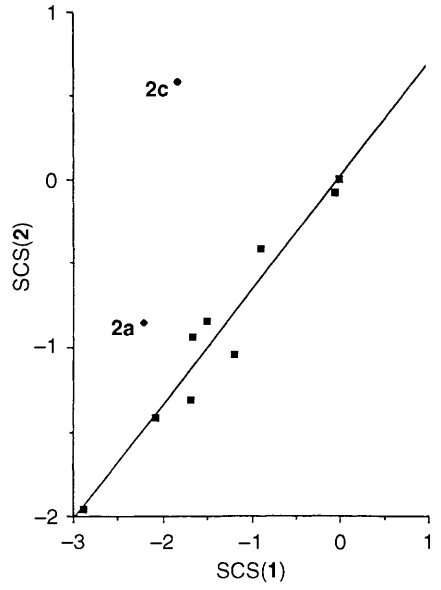


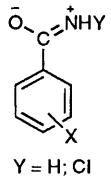
Fig. 1 SCS of C(α) of *N*-chlorobenzamides (**2**) *vs.* SCS of C(α) of benzamides (**1**)

the nature of the substituent (Z) attached to the carbonyl carbon.

This was clearly not the case for the benzamides (**1**) and *N*-chlorobenzamides (**2**) under study. Results in Fig. 1 and Table 3 show a significant diminution in sensitivity to substituents and in particular to the inductive component in *N*-chlorobenzamides (**2**). The change in ρ_I observed in the *N*-chlorobenzamide series strongly suggested that the π-polarization of the carbonyl group in benzamides, contrary to what has been previously observed,[2] is more sensitive to the substituent (Z) attached to the carbonyl carbon. The relative magnitudes of ρ_I and ρ_R indicated that π-polarization was the dominant substituent effect in *N*-chlorobenzamides.

Surprisingly *N*-chloro-4-nitrobenzamide (**2a**) and *N*-chloro-4-trifluoromethylbenzamide (**2c**) deviated from the line in Fig. 1. As noted above, the carbonyl carbons of the *N*-chlorobenzamides were uniformly shielded compared to the precursor benzamide. But within the series of *N*-chlorobenzamides these two substituents were less shielding than would have been predicted by the correlation line in Fig. 1. In the case of *N*-chloro-4-trifluoromethylbenzamide (**2c**), C(α) appeared significantly more downfield than would have been expected. Deviation from the line suggests a change in the nature of the interaction(s) with the carbonyl group.

The presence of the chlorine atom can affect the relative importance of the following resonance contributor:



Y = H; Cl

Conjugation of Y with the carbonyl carbon leads to shielding of C(α). As Y becomes more electron-withdrawing this resonance contributor becomes less favoured and ρ_R less negative (more positive).[1e] Table 3 confirms this prediction for *N*-chlorobenzamides (**2**) in general. In the case of *N*-chloro-4-nitrobenzamide (**2a**) and *N*-chloro-4-trifluoromethylbenzamide (**2c**) it is possible that this resonance contributor is even less favoured than in the other members of the series and as a result C(α) appears less shielded than would have been predicted.

There are several other possible explanations for the observed deviations. The torsion angle in 4-nitrobenzamide (**1a**) has been reported to be zero.[8] This has been attributed to a marked degree of conjugation between the nitro and amide groups. *N*-Chlorination could change the magnitude of this interaction. The trifluoromethyl group has been reported to behave anomalously.[3a,15] It is possible that in **2c** the CF_3 group was behaving anomalously compared to the other substituents used in this study. Further work is being carried out to determine the source of the deviations observed in Fig. 1.

The results of this study indicated that π-polarization plays the most important role in determining the ^{13}C chemical shift of C(α) in benzamides (**1**) and *N*-chlorobenzamides (**2**). It is proposed that recent results obtained in a study[1q] with benzamides and 2,6-dimethylbenzamides are not due to π-polarization being abnormally low but because the carbonyl group in benzamide derivatives is more sensitive to changes in the nature of the fixed substituents (*N*-chloro or ring methyl groups) present than the carbonyl group in the esters used for comparison purposes in that study and in the others[2] carried out to date.

Experimental

Benzamides **1a–k** were commercially available and used without further purification. ^1H NMR were recorded using a Bruker WM 360 operating at 360 MHz with $(CH_3)_4Si$ as the internal standard. Melting points were taken using a Mel-temp and are uncorrected. The percentage chlorine in the *N*-chlorobenzamides was determined by iodometric analysis.

Preparation of N-*Chlorobenzamides*.—N-Chlorination was carried out using a modified Altenkirk and Israelstam[13] procedure. The benzamide [except for 4-methoxybenzamide (**1k**)] was dissolved in the minimum amount of methanol and an equimolar amount of *tert*-butyl hypochlorite[16] was added. In the case of 4-methoxybenzamide (**1k**) the benzamide was dissolved in a solution of 5% w/w of borax in methanol.[13] The reaction mixture was kept in the dark until no starting material was evident by TLC (2–4 h). The reaction mixture was poured into water and the product isolated by filtration and dried overnight in a vacuum desiccator over potassium hydroxide. Products were recrystallized either from toluene or chloroform to avoid the use of benzene.[13] Iodometric analysis indicated 95+% chlorine content in the *N*-chlorobenzamides (**2**) prepared. The physical properties of all the previously reported *N*-chlorobenzamides agreed with the published[13] values. Previously unreported compounds are as follows.

N-Chloro-4-trifluoromethylbenzamide (**2c**) 88% yield, m.p. 188–190 °C, 99% Cl. *N*-Chloro-3-fluorobenzamide (**2e**) 31% yield, m.p. 110–112 °C, 98% Cl. *N*-Chloro-4-fluorobenzamide (**2h**) 67% yield, m.p. 173–176 °C, 98% Cl.

^{13}C *NMR Measurements*.—A solution containing a 25–50 mg sample of **2** and 1 cm^3 of $(CD_3)_2SO$ was prepared in a 5 mm sample tube. Spectra were obtained at 20 °C on a Bruker WM 360 spectrometer operating at 90.56 MHz, 32 K data points were collected over a spectral width of 21.7 kHz giving a digital resolution of 0.007 ppm.

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