^{17}O NMR study of substituent effects in 4-substituted *N*-chlorobenzamides and comparison with 4-substituted benzamides: sensitivity to ring substituents (ρ) reflects electronic and steric effects

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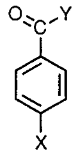
Natural abundance ^{17}O NMR spectra of 4-substituted *N*-chlorobenzamides were obtained in acetonitrile at 75 °C and compared with those for similarly substituted benzamides. An excellent correlation ($\delta = 5.43\sigma^+ + 350.1$, $r = 0.998$) was obtained when the ^{17}O chemical shifts of *N*-chlorobenzamides were plotted against σ^+ and using σ^- for the 4-nitro derivative. Based on the greater electronegativity of the *N*-chloro group the value of ρ observed for *N*-chlorobenzamides (5.4) would have been expected to be greater compared to that of benzamides (7.3). It is concluded that the ^{17}O chemical shift in *N*-chlorobenzamides is very sensitive to torsion angle and that is why a low value of ρ is obtained. Sensitivity (ρ) of the chemical shift to ring substituents cannot be used as an unambiguous measure of electronic effects in systems where the torsion angle is greater than zero.

Recently, one of us examined the transmission of substituent effects in benzamides and *N*-chlorobenzamides by ^{13}C NMR spectroscopy.[1] Natural abundance ^{17}O NMR[2] has also been used to study the transmission of substituent effects in benzamides.[3] To gain further insight into the transmission of substituent effects in benzamide derivatives a ^{17}O NMR study of 4-substituted *N*-chlorobenzamides was carried out and the results compared with those of similarly substituted benzamides.[4]

Benzamides and other aromatic carbonyl compounds are resonance hybrids of the contributing structures **A**–**D**. In ^{17}O NMR spectroscopy of aromatic carbonyl compounds the factors which most affect the sensitivity (ρ) of the chemical shift to ring substituents are: conjugation of Y with the carbonyl group (**D**) and the torsion angle between the side chain and the aromatic ring. Conjugation of the carbonyl group with the substituent Y shields the carbonyl oxygen and ρ decreases.[3c] In general, an increase in the electron demand of the carbonyl group increases ρ.[3c,d] ^{17}O NMR chemical shifts are very sensitive to steric effects and an increase in the torsion angle results in a decrease in the magnitude of ρ and a deshielding of the carbonyl oxygen.[3a,e,5,6]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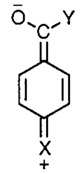
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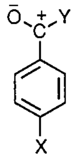
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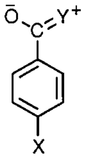
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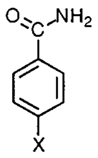
Results and discussion

Natural abundance ^{17}O NMR spectra of 4-substituted *N*-chlorobenzamides[1,7] **2** were obtained in acetonitrile at 75 °C. These values and those for 4-substituted benzamides[4] **1** are collected in Table 1.

Previous studies have found that the ^{17}O chemical shift values of aromatic carbonyl compounds correlate with σ^+ values.[3c–e] A good correlation ($\delta = 6.62\sigma^+ + 350.4$, $r = 0.981$) was obtained when the ^{17}O chemical shifts of *N*-chlorobenzamides were plotted against σ^+.[8] The point corresponding to the 4-nitro derivative deviated from the correlation line. An excellent correlation ($\delta = 5.43\sigma^+ + 350.1$, $r = 0.998$) was obtained when the σ^- value for the 4-nitro substituent was used (Fig. 1).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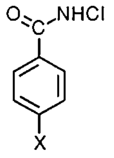
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X = NO_2; CF_3; Br; Cl; H; F; CH_3; OCH_3

Changing the Y substituent from NH_2 to the more electronegative NHCl group[1,9] would be expected to decrease the contribution **D** makes to the resonance hybrid.[10] This should lead to an increase in the magnitude of ρ.[3c,d] This was not observed in this study. A ρ value of 5.4 was obtained for *N*-chlorobenzamides and it can be compared to a value of 7.3 previously reported[3c] for benzamides. It should be noted that the value of ρ obtained for benzamides **1** is 6.3 when the correlation is carried out with the same substituents used in the *N*-chloro series and σ^- for the 4-nitro group.[11]

Recently, it was suggested[3e] that the relatively small value of ρ observed for benzamides[3c] might, in part, be caused by the torsion angles (28°)[3a] in this series of compounds. Therefore, the possibility that a change in the torsion angle was responsible for the lower than expected value of ρ noted in this study for *N*-chlorobenzamides was considered. Correlations between chemical shift and torsion angle (calculated by MM2) have been reported for aromatic amides and *N*,*N*-dimethylbenzamides[3a] and the slope of the correlation line has units of ppm/degree. This ratio can be used to obtain an approximate idea of how small changes in torsion angle can affect the value of ρ.

A change in ρ from 7 to 5 would be indicative of a proportionate contraction in the difference between compounds of highest and lowest chemical shift in a series (the chemical shift range). Assuming a chemical shift range of 10 ppm and using the previously reported value of 0.84 ppm/degree for the rela-

Table 1 ^{17}O NMR data (ppm) for benzamides (**1**) and *N*-chlorobenzamides (**2**) in acetonitrile at 75 °C[a]

Compd.[b]	δ	δ (other)[d]	Compd.	δ	δ (other)
4-NO_2 (**1a**)	334.1 (162)	578.0 (275)	4-NO_2 (**2a**)	356.8 (444)	579.6 (400)
4-CF_3 (**1b**)	330.9 (388)[c]		4-CF_3 (**2b**)	353.6 (365)	
4-Br (**1c**)	328.4 (135)		4-Br (**2c**)	351.2 (490)	
4-Cl (**1d**)	327.6 (118)		4-Cl (**2d**)	350.9 (471)	
H (**1e**)	326.3 (105)		H (**2e**)	350.0 (300)	
4-F (**1f**)	326.2 (100)		4-F (**2f**)	349.7 (390)	
4-CH_3 (**1g**)	324.1 (118)		4-CH_3 (**2g**)	348.3 (370)	
4-OCH_3 (**1h**)	321.9 (161)	55.1 (207)	4-OCH_3 (**2h**)	345.8 (350)	59.2 (604)

[a] Values in parentheses are the peak width (in Hz) at half height and the data collected in this study includes a 25 Hz exponential broadening factor. [b] Spectra for 4-substituted derivatives acquired in 0.5 M acetonitrile solutions at 65 °C. Measurements by Dr V. V. Toan, Lausanne, Switzerland.[4] [c] This study. [d] Chemical shift of other oxygen-containing groups present.

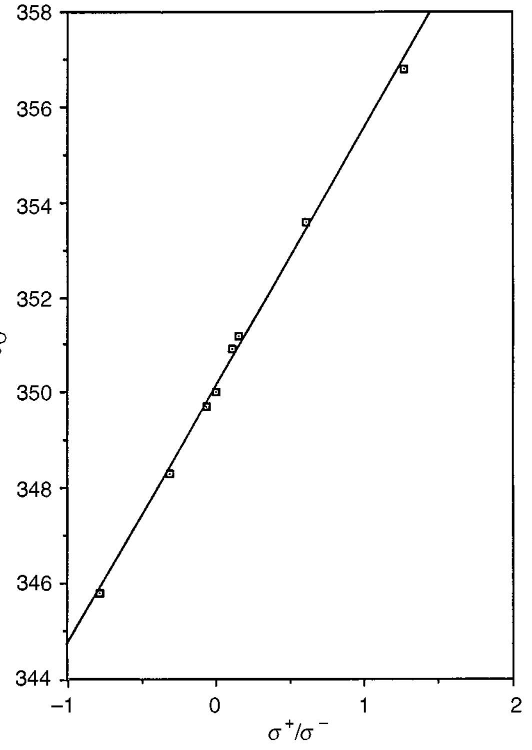

Fig. 1 ^{17}O chemical shift *vs.* σ^+ or σ^-

tionship between chemical shift and torsion angle[3a] for aromatic amides, the calculation (2/7)10 ppm/(0.84 ppm/°) = 3° shows that an increase of *ca.* 3° in torsion angle can cause ρ to drop from 7 to 5, all other factors remaining the same.[12] If *N*-chlorobenzamides are more sensitive to torsion effects than benzamides it would take a change of <3° in the torsion angle to explain the results observed in this study.

The result obtained above is approximate given that the chemical shift range of *N*-chlorobenzamides, in the absence of a change in torsion angle, is not known and the actual ppm/degree relationship for this series is also not known. But this calculation clearly illustrates that small changes in torsion angle are reflected in the magnitude of ρ.

In a previous ^{13}C NMR study of benzamides and *N*-chlorobenzamides it was concluded that the carbonyl group, in benzamides, is more sensitive to changes in the substituent Y than other aromatic carbonyl compounds.[1] Gassman's tool of increasing electron demand[3d,13] implies that those systems most sensitive to electronic effects would be precisely the ones most affected by small changes in their transmission. No steric effect was observed in the previous ^{13}C study.[1] Therefore, a greater sensitivity of the chemical shift to torsion angle in *N*-chlorobenzamides, rather than a slight change in torsion angle, is the likely reason why a lower than expected ρ is observed in this series of compounds.

Results of this study support the suggestion[3e] that the relatively low value of ρ previously observed in benzamides[3c,d] is in part a function of the torsion angle. Sensitivity (ρ) of the chemical shift to ring substituents cannot be used as an unambiguous measure of electronic effects in systems where the torsion angle is greater than zero.

Experimental

The preparation of the 4-substituted *N*-chlorobenzamides has been previously described.[1,7] ^{17}O NMR spectra were recorded on a Varian VXR-400 spectrometer equipped with a 10 mm broad-band probe. All spectra were acquired at natural abundance at 75 °C in acetonitrile (Aldrich, anhydrous gold label under nitrogen). The concentration of the compounds employed in these experiments was 0.5 M and were referenced to external deionized water at 75 °C. Butan-2-one reacted with *N*-chlorobenzamides and could not be used as the internal standard. The instrumental settings were: spectral width 35 kHz, 2K data points, 90° pulse angle (40 µs pulse width); 100 µs acquisition delay, 29 ms acquisition time. Typically, 40 000–80 000 scans were required. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.1 ppm by zero filling to 8K data points. The reproducibility of the chemical shift is estimated to be better than ±1 ppm.

Acknowledgements

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