# Stereoelectronic Effects on Anilide Conformation

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Secondary amides derived from *m*-substituted anilines show a measurable preference for the conformation with N–H *anti* to an electron-withdrawing *meta*-substituent.

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We observe differences between the chemical shifts of the 2- and 6-protons of certain *m*-substituted anilides [(**1**) $\rightleftarrows$ (**2**)] significantly greater than can be accounted for by the direct effects of the substituent X. Specifically, H(2) is more deshielded than expected, by an amount which appears to be related to the electronegativity of X (Table 1). These results recall the striking deshielding of the remaining *ortho*-proton observed for *o*-substituted anilides.[1—3] This was convincingly ascribed to the deshielding influence of the carbonyl group, held close to the *ortho*-proton as a result of hydrogen-bonding, as in (**3**). (The preferred conformation about the N–CO bond is well-known to be *Z* in normal amides.)[4] Clearly no such direct interaction is possible in the case of a *meta*-substituent.

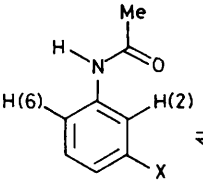
Our results might be explained if the relevant *m*-substituted anilides showed a preference for conformation (**1**), so that H(2) is selectively exposed to the deshielding effect of the amide C=O group. We report difference nuclear Overhauser effect (n.O.e.) experiments on four compounds which lend support to this interpretation.

Separate irradiation of the H(2) and H(6) signals of acetanilides (**1c**)—(**1f**) resulted in different positive n.O.e.s on the NH proton. The ratio of the areas under the two difference peaks was taken to be a measure of the conformer ratio (**1**) $\rightleftarrows$ (**2**), and thus of the free energy difference between the two forms (Table 1). Though it is difficult to achieve high precision in n.O.e. measurements, the magnitude of the conformational preference clearly depends on the nature of the substituent X in a rational way, as shown by the correlation with $\sigma_m$ (Figure 1): increasing electron-withdrawal favouring the conformation (**1**) with the N–H *anti* to the substituent. These results in

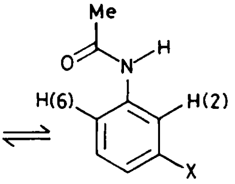
**Table 1.** $^1$H N.m.r. data for *m*-substituted anilides (**1**).[a]

| Compound | $\delta_{H(2)}$ | $\delta_{H(6)}$ | $\Delta\delta$/ p.p.m.[b] | $\Delta\delta_{corr}$[c] | $\Delta G°$/ kJ mol$^{-1}$ [d] |
|---|---|---|---|---|---|
| (**1a**) | 7.65 | | 0 | 0 | 0 |
| (**1b**) | 7.49 | 7.45 | 0.04 | 0.02 | —[e] |
| (**1c**) | 7.42 | 7.14 | 0.28 | 0.32 | 0.21 ± 0.11 |
| (**1d**) | 7.90 | 7.45 | 0.45 | 0.33 | 0.82 ± 0.07 |
| (**1e**) | 8.16 | 7.82 | 0.34 | 0.26 | 0.64 ± 0.06 |
| (**1f**) | 8.71 | 7.93 | 0.78 | 0.21 | 1.18 ±0.17 |

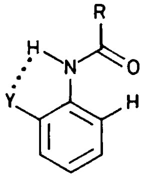
[a] Measured in [$^2H_6$]-acetone at 250, 360, or 400 MHz, at 20 mg/ml; results appear to be independent of concentration. [b] Difference in chemical shift between H(2) and H(6). [c] Difference between measured and calculated $\Delta\delta$, assuming standard effects of substituents (ref. 9). [d] Calculated as described in the text, using means of results from 4, 5, 4, and 3 experiments for X = OMe, Cl, CN, and $NO_2$, respectively. [e] Signals too close for selective irradiation.



(**1**)



(**2**)



(**3**)

**a**; X = H
**b**; X = Me
**c**; X = OMe
**d**; X = Cl
**e**; X = CN
**f**; X = $NO_2$

solution are mirrored in the solid state: of 16 anilides with electron-withdrawing *meta*-substituents whose structures are available from our own work or from the Cambridge Structural Database,[5] 13 crystallise in the same conformation (**1**).

There seems little doubt that we have identified a small but significant stereoelectronic effect. Similar effects of remote substituents on the conformations of anisole and enol ether OMe groups have been interpreted in terms of a more favourable $n$–$\sigma^*$ interaction, of a non-bonding electron-pair on oxygen with the C–C $\sigma$-bond affected by the adjacent electronegative substituent.[7,8] In the case of anilides (**1**) the N–H $\sigma$-bonding orbital is a better donor than $\sigma_{N-CO}$, and $\sigma^*_{C(1)-C(2)}$ a better acceptor than $\sigma^*_{C(1)-C(6)}$, because of the electron-withdrawing substituent at C(3).

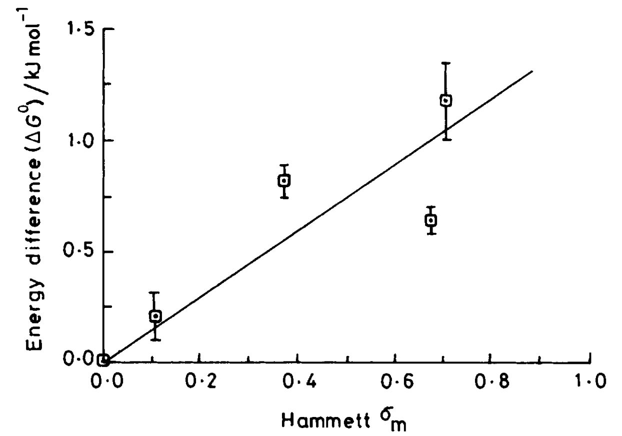


**Figure 1.** Hammett plot of conformational preference ($\Delta G°$, Table 1) *vs.* $\sigma_m$ for the substituent X for anilides (**1**). Error bars represent 95% confidence limits.

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## References

1 A. Ribera and M. Rico, *Tetrahedron Lett.*, 1968, 535.
2 B. D. Andrews, I. D. Rae, and B. E. Reichert, *Tetrahedron Lett.*, 1969, 1859.
3 G. W. Gribble and F. P. Bousquet, *Tetrahedron*, 1971, **27**, 3785.
4 P. Chakrabarti and J. D. Dunitz, *Helv. Chim. Acta*, 1982, **65**, 1555.
5 Ten compounds from the Cambridge Structural Database[6] (ref. codes ACBUOL, FAPFAD, GLYXAN, DCIBAN, MPIPAN, PDACAM, PIPBAN, RAFXND, ICSALA, MPIPCA), six unpublished structures (P. Camilleri, P. G. Jones, A. J. Kirby, R. J. Lewis, P. R. Raithby, and D. J. Williams, unpublished work).
6 F. H. Allen, O. Kennard, and R. Taylor, *Accts. Chem. Res.*, 1983, **16**, 146.
7 J. K. M. Sanders and B. K. Hunter, 'Modern N.M.R. Spectroscopy,' Oxford University Press, Oxford, 1987, p. 203.
8 A. J. Kirby, 'The Anomeric Effect and Related Stereoelectronic Effects at Oxygen,' Springer Verlag, Berlin, 1983, p. 74.
9 E. Pretsch, T. Clerc, J. Seibl, and W. Simon, 'Tables of Spectroscopic Data for Structure Determination of Organic Compounds,' translated by K. Biemann, Springer Verlag, Berlin, 1983.