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Short Research Article

Origin of the large isotope-induced shift in the ^{1}H-NMR of *ortho*-^{2}H-labelled anilides†

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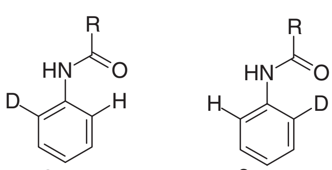
Introduction

Isotope effects associated with the introduction of deuterium into a molecule are conveniently investigated using both ^{1}H- and ^{13}C-NMR.[1] We recently reported an isotopic shift for the remaining *ortho* proton of *ortho*-^{2}H anilides[2] which was very large, 16 ppb upfield in $CDCl_3$ at 298 K.



1 2

The deshielding effect of the carbonyl group on the *o*-proton of anilides affords a sensitive probe for conformation about the N–Ar bond and such chemical shifts have been used to investigate the conformations of mono-*ortho*[(2a–c)] and mono-*meta*[(2d)]-substituted anilides, hence we ascribed the origin of the effect to a small preference for conformer **2** over conformer **1**.[3] The results of variable temperature NMR studies of one such system, *ortho*-^{2}H acetanilide,[4] in three solvents are now reported.

Results and discussion

The effect of temperature on conformational preferences can be calculated[5] and the results compared with the experimental data from variable temperature NMR studies to provide estimates of the relative populations of the two conformers together with the enthalpy and entropy variation between them (Table 1).

In all cases ΔS for the process approximated to zero (and hence was assumed to be zero for modelling purposes) whilst ΔH was of the order of -133 J/mol for a non-polar solvent, toluene, to -53 J/mol for a polar solvent, acetonitrile. Hence, the data clearly suggest that the position of equilibrium is enthalpy driven. Moreover, the decrease in ΔH with increasing solvent polarity argues strongly for an electronic rather than steric origin. The effect may reflect different dipole–dipole,[6,7] non-bonding-orbital[2d] or H-bonding[2b] interactions Though similar effects have previously been advanced as explanations[8] for anomalous isotopic shifts, to our knowledge this is the first direct experimental evidence for an electronically mediated conformational effect arising from a single D-atom substitution.

Table 1 Thermodynamic parameters and populations of conformer 2 for [2-^{2}H] acetanilide, in three NMR solvents at 298 K

Solvent	ΔH (J/mol)	ΔS (J/K mol)	Population of conformer 2 (% at 298 K)
[^{2}H]Toluene	−118 to −147	ca. 0	51.2–51.5
[^{2}H]Dichloromethane	−66 to −83	ca. 0	50.7–50.8
[^{2}H]Acetonitrile	−47 to −59	ca. 0	50.5–50.6

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4. *o*-Chloroacetanilide (104 mg) in THF (2 ml) containing Et_3N (125 μl) and 5% Pd on $CaCO_3$ (30 mg) was deuterogenated for 18 h. Work up yielded [2-^{2}H]acetanilide (crystals from boiling 10% MeOH/water, 88% *o*-^{2}H, mp 114–115°C. Lit. 113–115°C.
5. $\Delta\delta = (\delta_1 - \delta_2)(K-1)/2(K+1)$ where; $\Delta\delta$ = observed shift, δ_1 = chemical shift of an *ortho* proton *syn* to carbonyl, δ_2 = chemical shift of an *ortho* proton *syn* to NH, K = the equilibrium constant [itself variable via $K = e^{(\Delta S/R - \Delta H/RT)}$]. Estimation of $(\delta_1 - \delta_2)$ from NH acylation studies[2b] and conformationally rigid systems are in agreement with the 1.6–2 ppm used in this study.
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