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TEMPERATURE DEPENDENCE OF ^{19}F CHEMICAL SHIFTS IN SUBSTITUTED BENZYL FLUORIDES.

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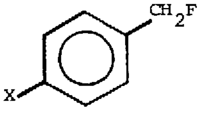
Abstract- The ^{19}F chemical shifts of substituted benzyl fluorides are shown to be temperature dependent and this is discussed in terms of conformational effects.

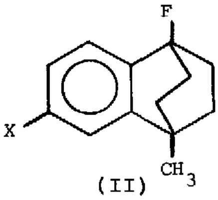
It has been known for some time that ^{19}F NMR chemical shifts in benzyl fluorides (I) are sensitive to the effects of substituents[1,2]. The apparent anomaly concerning the direction of response to substituent effects has yet to be resolved[2]. Thus, the effect of electron donating (withdrawing) substituents is to cause a downfield (upfield) shift in contrast to the expected upfield (downfield) shift. The expected direction is observed in other fluorine series[3,4], including substituted fluorobenzenes[3], where explanations of the shifts in terms of the electronic effects of the substituent are well established[5].

One difficulty which has so far prevented delineation of the factors which determine the benzyl fluoride shifts is the non planar nature of the CH_2F probe group which prevents a meaningful separation of the sigma and pi components of electron density about the fluorine. The importance of separating these individual components of electron density has been shown for the fluorobenzenes and benzoyl fluorides[4], where pi density changes provide the best fit to the observed chemical shifts.

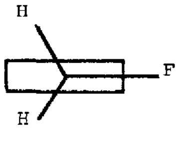
Another difficulty concerns the possibility of conformational mobility of the CH_2F group. In this communication we present evidence from a variable temperature ^{19}F NMR study which suggests that conformational changes have a profound influence on substituent chemical shifts (SCS) in this series. Recent data on a conformationally rigid model system (II) related to the benzyl fluorides in which the C-F bond is fixed in the plane of the benzene ring also confirms this view[6]. In that model system, the SCS values were reduced to an extremely small magnitude compared with benzyl fluorides themselves.



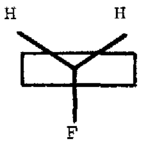
(I)



(II)



(III)
cis



(IV)
orthogonal

Chemical shifts were measured at various temperatures using 2000 Hz spectral widths. The data was recorded for dilute (1% w/v) solutions in d6 acetone and the shifts were measured in Hz directly from the carrier frequency for samples locked to the deuterium signal of solvent. This proceedure was checked by remeasuring some data relative to internal tetrachlorotetrafluoro cyclobutane reference, which showed very little temperature dependence. In Figure 1 it can be seen that the chemical shift varies dramatically with temperature and substituent. The trends shown in the figure are consistent with changes in the relative populations of the contributing conformers. Thus, if we consider only the two extreme conformers (the cis (III) and orthogonal (IV) forms shown above), then, as the temperature is lowered, the relative populations of these conformers will alter. The variation in population with temperature will depend upon the energy difference between the two forms. The changes in chemical shift with temperature indicates that the cis and orthogonal forms have different absolute chemical shifts (and hence different substituent chemical shifts).

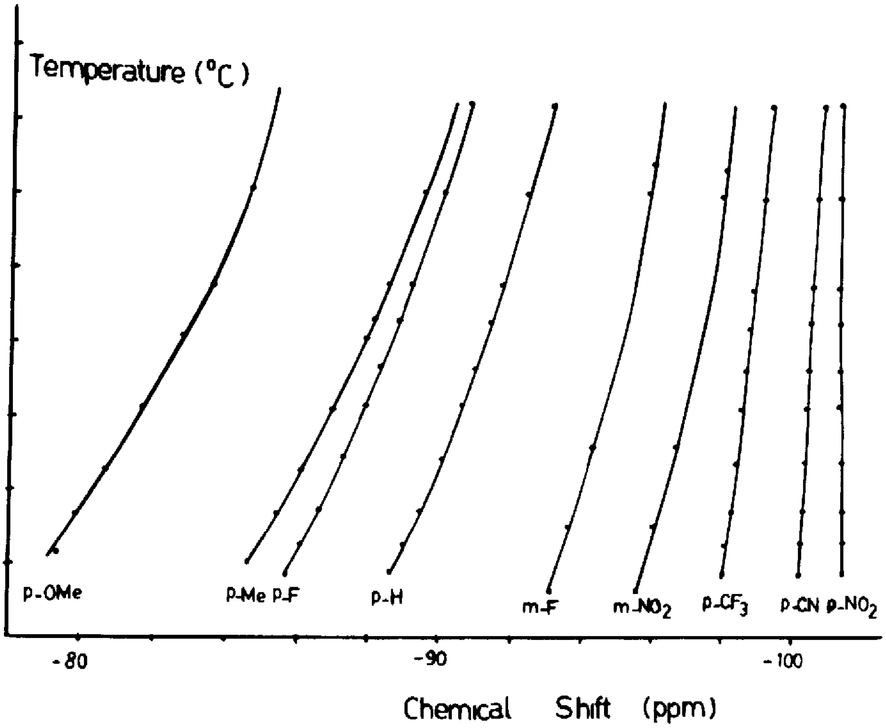
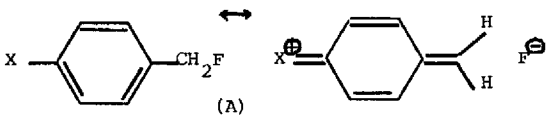
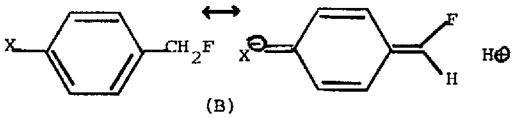


Fig 1. Variation in Chemical Shift (in ppm. from tetrachlorotetrafluoro cyclobutane) with Temperature.

Ab initio (STO-3G) calculations in Table 1 show that the energy difference (ΔE) between the two forms varies with the para substituent. Whilst the absolute values of these barriers may not be correct, there is evidence that the trend upon substitution does accurately reflect the actual trends. Precedence for the reliability of STO-3G calculations in predicting the effects of substituents on energy barriers has been set in a study of p-phenols[7]. The energy barriers expressed relative to the hydrogen substituent ($\delta\Delta E$), correspond to the resonance effect of the para substituent. Thus, for strong donors, there will be a tendency for some enhancement of the hyperconjugative acceptor interaction shown below (A). This interaction is maximized when the C-F bond is orthogonal to the plane of the benzene ring, and hence the preference for donors to favor the orthogonal form.



(A)



(B)

When X is an acceptor the hydrogen hyperconjugative interaction above (B) becomes important and this is maximized when the hydrogen atoms are out of the plane of the ring. This is reflected in the tendency of acceptors to favor the cis conformation. This conclusion is also supported by frontier molecular orbital arguments which show that electron donation favors the fluorine out of plane, whilst electron withdrawal favors the fluorine in plane[8].

Table 1. Energy differences between cis and orthogonal forms of p-benzyl fluorides*, and Substituent Chemical Shifts at +22,-80 °C.

P-X	ΔE(kcal/mol)	δΔE(kcal/mol)	SCS** (+22° C)	SCS (-80° C)
NH_2(pl)	-0.16	-0.42		
OH (OMe)	0.06	-0.21	7.57	8.95
F	0.07	-0.19	2.36	2.89
CH_3	0.17	-0.09	2.83	3.61
H	0.26	0.00	0.00	0.00
CF_3	0.44	+0.17	-6.53	-9.18
CN	0.57	+0.30	-8.12	-11.43
NO_2	0.70	+0.44	-8.78	-12.69

* A positive value denotes that the cis form is more stable.

** Substituent chemical shift at the indicated temperature (positive shifts are downfield).

When the data in this Table is compared with Figure 1 it can be seen that the variation in shift with temperature is greatest for those para groups which relatively favor the orthogonal conformation. The variation in temperature dependence for the different compounds appears therefore to be a reflection of different degrees of conformational mobility. Based on the assumption that the temperature variation of chemical shift is due to a variation in the relative populations of cis and orthogonal forms, and that the observed shift is a weighted average of the shifts of the separate forms, then it follows that a change in the sign of ΔE should be reflected in a change in the direction of the slopes. The plot for the p-NO_2 series curves slightly in the opposite direction to the other series, suggesting that it has an energy barrier opposite in sign. ie. either the p-NO_2 compound prefers the cis form and the other compounds the orthogonal, or the p-NO_2 prefers the orthogonal, and the others the cis. The former explanation is the likely one, based on the logic presented above (which is supported by the calculations) regarding the expected substituent effect on energy barriers in this series. We therefore suggest that the calculated energy barriers should all be scaled by subtraction of about 0.7 kcal/mol. This means that benzyl fluoride itself is predicted to favor the orthogonal form by 0.4 kcal/mol. There has been no clear cut determination of the preferred conformation of benzyl fluoride, although our suggestion is contrary to the conclusions of other workers[9] .

That the observed temperature dependence is due to a conformational process, and not to other effects such as intermolecular associations was determined from a concentration study performed in conjunction with the variable temperature analysis. This data indicated that at low concentrations there was very little variation in chemical shift with concentration for benzyl fluoride itself. The temperature dependence also cannot be attributed to special solvent related effects, as we have observed similar behaviour in the more inert solvent $CDCl_3$. Conformational effects of the substituent X itself were also discounted on the basis of experiments involving a temperature study in fluorobenzene derivatives. The large temperature variation in the p-H, p-F benzyl fluorides also excludes the hypothesis that the temperature dependence is due to conformational changes in the X group.

The SCS results fit the DSP equation[10] with very good precision both at room temperature, and at low temperatures (eqs. 1 and 2) (The SCS data is in Table 1).

$$+20\ \mathrm{C}^{\circ}\quad \mathrm{SCS} = -9.3\sigma_I - 22.1\sigma_R{}^{0}\quad f = 0.08 \qquad (1)$$

$$-80\ \mathrm{C}^{\circ}\quad \mathrm{SCS} = -13.7\sigma_I - 28.0\sigma_R{}^{0}\quad f = 0.05 \qquad (2)$$

As the SCS values in this series at a given temperature are a function both of the electronic effects of X, and the conformation of the probe group (CH_2F), then, from the excellent fits of equations (1) and (2), it follows that conformational changes of the probe group are related closely to the electronic effect of X.

Our interpretation of the observed temperature dependence of ^{19}F chemical shifts in this series provides a novel and important means of verifying energy barriers to rotation for fluorinated sidechains. This is particularly so for relatively small energy barriers. Our data supports the conclusions of Adcock[6] that the out of plane component of the C-F bond is responsible for the large reverse SCS effects in this series. The larger SCS effects seen in equation (2) relative to (1) indicate that at the lower temperature where there is a greater out of plane contribution, the reverse SCS effects are larger. We suggest that the in plane contribution to SCS is normal and small, whilst the out of plane contributon is reverse and larger. Detailed examinations of solvent, temperature and concentration effects on other fluorinated series are in progress.

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